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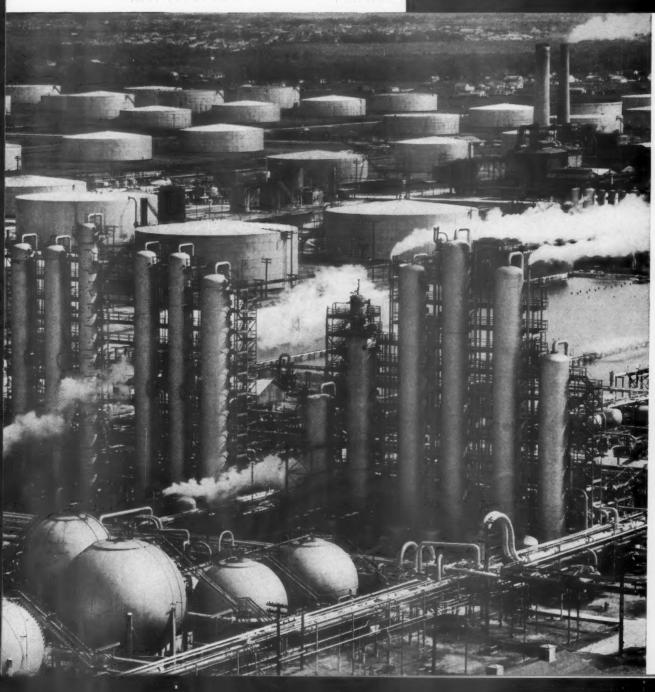
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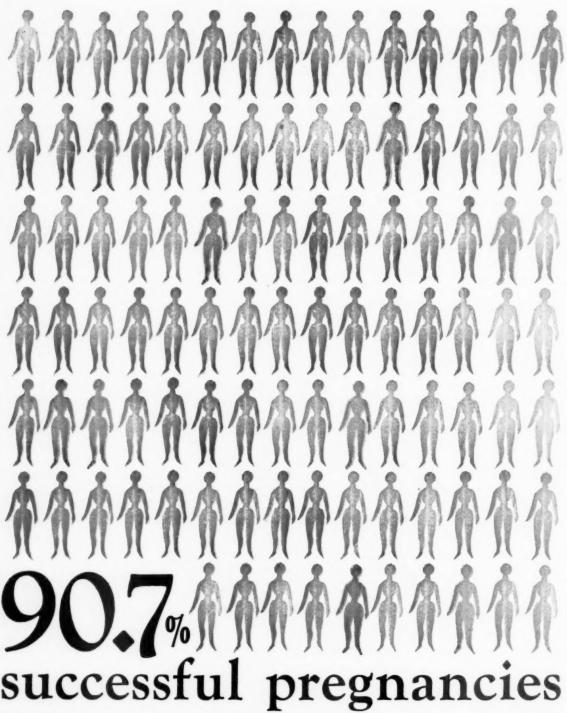
Vol. XXVIII FEBRUARY 1960 No. 2

CONTENTS

0001120110	
Editorial	
Renal Acidosis J. Russell Elkinton	165
Clinical Studies	
The Diagnosis and Treatment of Renal Hypertension. With Special Reference to a Case of Hypertension Due to Stenosis of Both Renal Arteries E. R. YENDT, W. K. KERR, D. R. WILSON AND Z. F. JAWORSKI	169
There has been a lively resurgence of interest in surgical correction of renal hypertension resulting from anomalies reproducing the Goldblatt phenomenon, and the present study validates this interest. The authors recount their experience with twenty patients subjected either to nephrectomy or, when feasible, to renal artery repair for relief of renal hypertension. The diagnosis, which requires a high index of suspicion, was based for the most part on differential studies of urinary volume and sodium excretion by the two kidneys and/or on aortography; the usual methods of examination of renal function do not suffice. Three of the patients, one described in detail, had bilateral renal artery stenosis. It is considered that surgical intervention was successful in twelve of the twenty patients, all presumed to be retractory to medical therapy. However, success in diagnosis and management, as is made abundantly clear, requires meticulous attention to detail in both medical and surgical aspects of patient care.	
Effect of Thoracolumbar Sympathectomy on the Clinical Course of Primary (Essential) Hypertension. A Ten-year Study of 100 Sympathectomized Patients Compared with Individually Matched, Symptomatically Treated Control Subjects Kenneth A. Evelyn, Madan M. Singh, William P. Chapman,	
GEORGE A PERERA AND H THATER	188

This collaborative, large scale, long term study of the effects of thoracolumbar sympathectomy on the course of essential hypertension omits no device, in experimental design or in statistical analysis, to achieve an impartial and objective evaluation. The results of a ten-year follow-up of 100 surgically treated patients are compared with those of 100 matched control subjects treated symptomatically, i.e., without antihypertensive drugs. The findings are thus of interest in respect to the natural history of essential hypertension, which is described in some detail as well as in connection with the results of sympathectomy. The data are in general agreement with previous reports but are more complete and, in some respects, disillusioning. Surgery convincingly reduced hypertension (average decrease, 21 mm. Hg systolic, 15 mm. Hg diastolic) and with this, papilledema and retinopathy, probably also had some preventative effect on renal deterioration. There was no significant difference between the surgically and medically treated patients, however, in the incidence of cardiac failure, myocardial infarction, cerebrovascular accidents, mean survival

Contents continued on page 5



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*Murphy, H. S., et al., Scientific Exhibit, A.M.A., Dec. 1-4, 1959, Dallas, Texas.

CONTENTS continued-February 1960

VOLUME TWENTY-EIGHT

NUMBER TWO

time or mortality rate (41 per cent of the surgical series dead at the end of ten years, 47 per cent of the control subjects). Thoracolumbar sympathectomy has an unquestioned place in the management of essential hypertension but, balancing up postoperative gains against disabilities, the authors conclude that "the over-all effect of the operation on morbidity and mortality in this small consecutive series of cases was somewhat disappointing."

Testicular Lesions of Periarteritis Nodosa, with Special Reference to Diagnosis Elmer V. Dahl, Archie H. Baggenstoss and James H. DeWeerd 222

In view of the uncertainties of muscle biopsy as a means of diagnosis in periarteritis nodosa, the suggestion of testicular biopsy in appropriate cases is of interest. The suggestion is based on the substantial incidence of testicular lesions found at autopsy, and the authors predict that some 20 per cent of testicular biopsies in patients with periarteritis nodosa should yield diagnostic results. This is not recommended as a routine procedure but when testicular symptoms are or have been present.

Aldosterone Excretion in Hypopituitarism and After Hypophysectomy in Man E. J. Ross, W. van't Hoff, J. Crabbé and G. W. Thorn 229

There has been some difference of opinion as to the complete corticotropin-independence of aldosterone excretion, and of the effects of hypophysectomy. These differences are resolved, in part, by the present study. Patients with panhypopituitarism of long standing excrete significantly less than normal quantities of aldosterone in the urine but for some time after hypophysectomy may show enhanced aldosterone excretion, in association with the large volumes of urine passed (diabetes insipidus). It is assumed that the adrenotropic effect of corticotropin maintains the capacity of the adrenal cortex to form and release aldosterone in greater or lesser measure.

Hyperventilation and Arterial Hypoxemia in Cirrhosis of the Liver H. O. Heinemann, C. Emirgil and J. P. Mijnssen 239

Arterial hypoxemia and hyperventilation were shown by the authors to be present simultaneously in patients with cirrhosis of the liver. Careful pulmonary function studies excluded diffusing difficulty as an explanation for the hypoxemia. An increase in venous admixture, best explained by assuming portal to pulmonary vein anastomoses, is advanced as the mechanism for the hypoxemia. Careful analysis of the factors affecting pulmonary ventilation failed to reveal any satisfactory explanation for the hyperventilation observed.

Coincidence of Patent Ductus Arteriosus and Rheumatic Heart Disease, with a Comment on the "Postcommissurotomy Syndrome"

JOHN A. BOONE AND ROBERT M. ROSEMOND 247

The development of what appears to be overt rheumatic heart disease in an appreciable proportion of patients operated on for patent ductus arteriosus suggests a predilection for rheumatic fever under these circumstances, as would seem to be true of many congenital heart anomalies. The point stressed is that postoperative observation should be particularly alert to the possibility of rheumatic heart disease, and that perhaps regular antibiotic prophylaxis should be instituted.

Contents continued on page 7

new for total management of itching,¹² inflamed,^{3,4} infected^{5,6} skin lesions



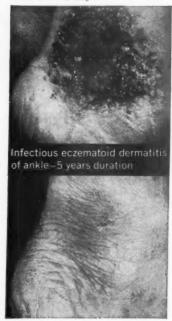
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Reviews

Chronic Active Pulmonary Histoplasmosis with Cavitation. A Clinical and Laboratory Study of Thirteen Cases

DAVID F. LOEWEN, JOHN J. PROCKNOW AND CLAYTON G. LOOSLI 25

While it is generally appreciated that pulmonary histoplasmosis may follow a prolonged active course, with cavitation, and closely simulate tuberculosis, detailed documentation has been sparse. This is amply provided in the present study, which summarizes the case histories of thirteen such patients. It is readily understandable from the history, physical findings and roentgenograms of these cases that they are commonly confused with tuberculosis. The differential diagnosis can be established only by demonstration of histoplasmic infection by means of skin tests, serological reactions or (conclusively) by culture of the fungus. Failure to demonstrate acid-fast bacilli should lead to suspicion of fungal infection, but since many patients are consigned to tuberculosis sanatoriums in error, they are likely to contract tuberculosis there if not already infected.

The Postpneumonectomy State. Clinical and Physiologic Observations in Thirty-Six Cases

Benjamin Burrows, Robert W. Harrison, William E. Adams, Eleanor M. Humphreys, Edwin T. Long and Arthur F. Reimann 281

Extensive pulmonary resection has become an important therapeutic measure in recent years, and the adequacy of pulmonary function after pneumonectomy is therefore a question of some practical significance. The present study is one of relatively few performed in adults sufficiently long after ablation of the lung. Pulmonary overinflation in the remaining lung was commonly observed but did not, in the majority of patients, result in significant exercise intolerance, or in destructive changes in the remaining lung. When respiratory difficulty was encountered, it was attributed to a complicating cardiac or pulmonary disorder. Of considerable physiologic interest was a demonstrable reduction in diffusing capacity. As a result of pneumonectomy, the cardiac output passed through the remaining lung but this did not result in significant pulmonary hypertension unless the remaining lung was abnormal.

Clinicopathologic Conference

Severe Abdominal Pain with Negative Physical and Laboratory Findings 298

Clinicopathologic Conference (Washington University School of Medicine).

Case Reports

Primary Aldosteronism. A Case with Severe Hypertension
I. Gabe, H. I. Jory, Lily Mulligan and J. W. Woollen 311

A well studied and instructive case of unusual interest.

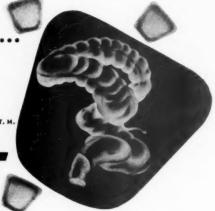
Contents continued on page 9

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CONTENTS continued-February 1960

VOLUME TWENTY-EIGHT

NUMBER TWO

- Multiple Myeloma Manifested as a Problem in the Diagnosis of Pulmonary Disease

 EDWARD A. FAVIS, HERBERT D. KERMAN AND WILLIAM SCHILDECKER 323

 An informative case.
- Postural Hypotension. Report of a Case, with Hemodynamic Studies of Central, Peripheral and Pulmonary Artery Pressures

ALAN SOLOMON AND LESLIE A. KUHN 328

An interesting case.

Advertising Index on Page 165

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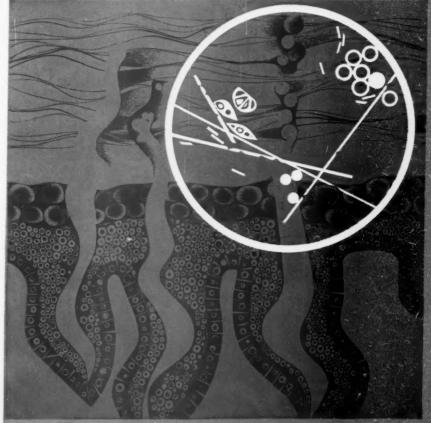
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References:
1. Fox, H. H.: Antibiotic Med. & Clin.
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Streptomycin	2879	943	(32.8%)	368	(12.8%)	1568	(54.4%)
Sulfisoxazole	1730	452	(26.1%)		-	1278	(73.9%)

"In order of decreasing effectiveness, the activity of the drugs against gram-negative organisms was as follows: nitrofurantoin, chloramphenicol, tetracycline, streptomycin, and sulfisoxazole."

OVER-ALL RESPONSE OF GRAM-POSITIVE BACTERIA TO ANTIMICROBIAL DRUGS3

	No. organis tested		No.sensitive (%)		No. moderately resistant(%)		No.resistant (%)	
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Penicillin		2353	515	(21.9%)	303	(12.9%)	1535	(65.2%)
Erythromycin		2353	1633	(69.4%)	308	(13.1%)	412	(17.5%)
Tetracycline		2353	987	(41.9%)	673	(28.6%)	693	(29.5%)
Chloramphenicol		1939	1593	(82.2%)	242	(12.5%)	104	(5.3%)
Sulfisoxazole		303	25	(8.3%)		-	278	(91.7%)

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results with analexin in clinical trials

Batterman, Grossman and Mouratoff⁵ compared Analexin with aspirin, sodium salicylate and a placebo in a series of 195 patients with various painful conditions. The authors concluded:

"Not only is satisfactory relief of painful states achieved in the majority of patients regardless of etiology and duration of pain, but there is also no evidence suggestive of cumulative toxicity. Furthermore, in contrast to codeine and meperidine, the likelihood of untoward reactions occurring in ambulant patients is not high. This is a decided advantage since the control of pain in the ambulant patient with chronic pain is a major clinical problem."

"Phenyramidol (Analexin), with therapeutic doses is not only safe for chronic administration, but also to date we have noted no adverse effect upon the cardiovascular, gastrointestinal, respiratory, kidney, liver or central nervous systems."

Wainer⁰ reported a series of 200 cases treated with phenyramidol for various painful conditions. In fifty of these patients who had dysmenorrhea, he saw excellent results in 40, good results in 5 and poor results in 5. Further examination in 4 cases not responding revealed presence of organic pathology. A second group of 50 cases with headache and associated premenstrual tension responded with over-all excellent results. Wainer also reports the use of phenyramidol to replace codeine for postpartum pain and describes 100 cases wherein a combination of phenyramidol with aluminum aspirin (Analexin-AF) successfully replaced aspirin and codeine therapy.

more results with analexin in clinical trials

In another series of dysmenorrhea cases, Bader⁷ compiled data on 20 employees of a telephone company who required ½ to 2 days off from work every month regardless of prior therapy employed. Satisfactory results were achieved in 15 out of 20 and a fair response in the remaining five. All were able to remain on the job although relief was not complete in the latter cases.

Bealer⁸ treated 32 patients with phenyramidal mostly for musculoskeletal disorders and had good or very good results in 15, fair results in 14 and poor or inconclusive results in 2 patients. Cohen used phenyramidal together with aspirin in 15 patients with such conditions as sciatic pain, osteoarthritis, anterior chest wall syndrome, etc. and got outstanding relief in 80 per cent. Gilbert¹⁰ reported that 15 patients with nonspecific headache had excellent relief in a matter of minutes with phenyramidol, and in 8 cases of dry socket pain Bruno¹¹ reports immediate relief in six cases and good results later in the other two after sockets were curetted under local anesthesia. Stern¹² reported on 40 ambulatory cases with a variety of painful conditions and saw good relief in 32 patients and poor in 8. Results were best in acute sacroiliac pain, myositis, muscle spasm, fractures, pleurisy and neuritis. Ten of 13 patients with osteoarthritis responded very well and are continuing on phenyramidal therapy.

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for relief of pain and muscle tension in: low back pain sprains and strains myalgia glass arm wry neck osteoarthritis dysmenorrhea tension headache gout postpartum pain epigastric distress (pylorospasms, gastritis, duodenal ulcer, cholecystitis) genitourinary conditions (premenstrual cramping or tension) abdominal distress (flatulence, colic) toothache and dry socket pain

analexin-AF (phenyramidol with aluminum aspirin)

for relief of pain and muscle tension also involving inflammatory processes and/or fever, as in: arthritis arthralgia bursitis tendinitis myalgia of strain and tear pre- and postoperative toothache

dosage:

analexin: for relieving pain and/or muscle tension, one or two tablets every 4 hours. In dysmenorrhea, two tablets initially then one tablet every 2 to 4 hours as needed.

analexin-AF: two tablets every 4 hours or as required.

supply:

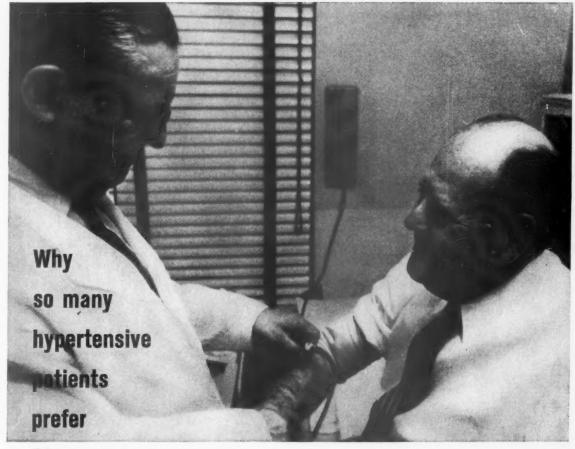
analexin tablets—Each tablet contains 200 mg. of phenyramidol HCI. Bottles of 100 tablets.

analexin-AF tablets - Each tablet contains 100 mg. of phenyramidol HCl and 300 mg. of aluminum aspirin. Bottles of 100 tablets.

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Read before the New York Academy of Sciences, Dec. 5, 1959. 7. Bader, G.: Clinical Report
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596. 10. Gilbert, E: Clinical Report 511; 597. 11. Bruno, E. A.: Clinical Report 511; 593.
12. Stern, E.: Clinical Report 511; 599.

Clinical Reports cited above are in the files of the Medical Department, Irwin, Neisler & Co.

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It spares them from the usual rauwolfia side effects

FOR EXAMPLE: "A clinical study made of syrosingopine [Singoserp] therapy in 77 ambulant patients with essential hypertension demonstrated this agent to be effective in reducing hypertension, although the daily dosage required is higher than that of reserpine. Severe side-effects are infrequent, and this attribute of syrosingopine is its chief advantage over other Rauwolfia preparations. The drug appears useful in the management of patients with essential hypertension."*

*Herrmann, G. R., Vogelpohl, E. B., Hejtmancik, M. R., and Wright, J. C.: J.A.M.A. 169:1609 (April 4) 1959.



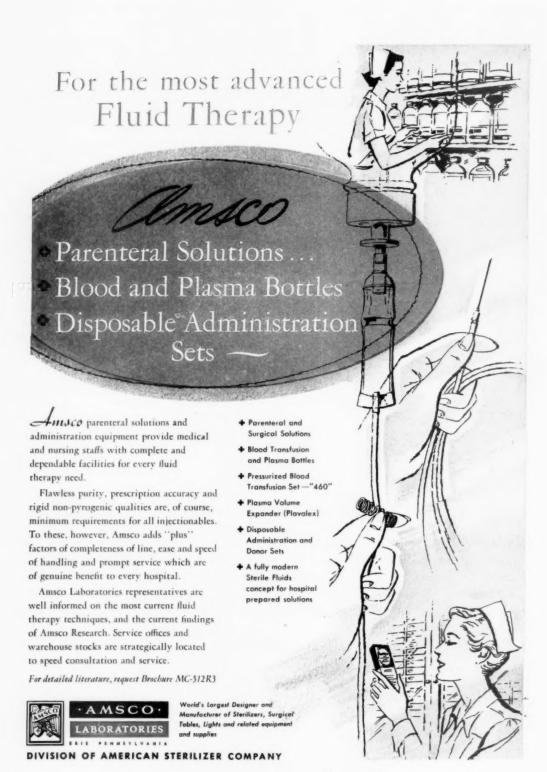
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First drug to add in hypertensive patients already on medication

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Tablets: Penicillin V Potassium, Wyeth Wyeth Laboratories, Philadelphia 1, Pa.

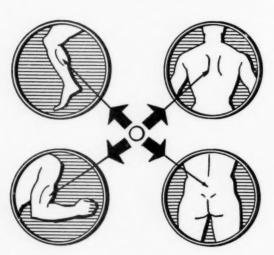


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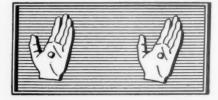
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ADVANTAGES

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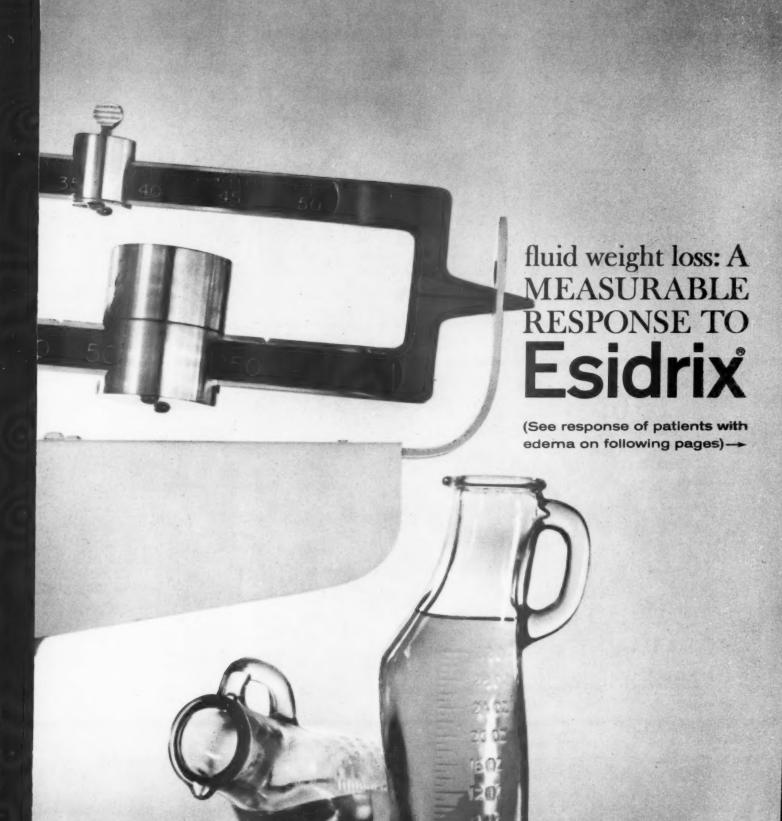
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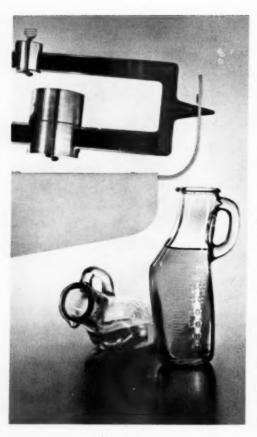






10 pounds lost; pitting edema cleared in 5 days; copious urine output, yet serum electrolytes remained within normal range

important reasons why physicians choose Esidrix for congestive heart failure, toxemia & edema of pregnancy, premenstrual edema, steroid-induced edema, edema of obesity



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improved analog of chlorothiazide, a product of CIBA research CIBA

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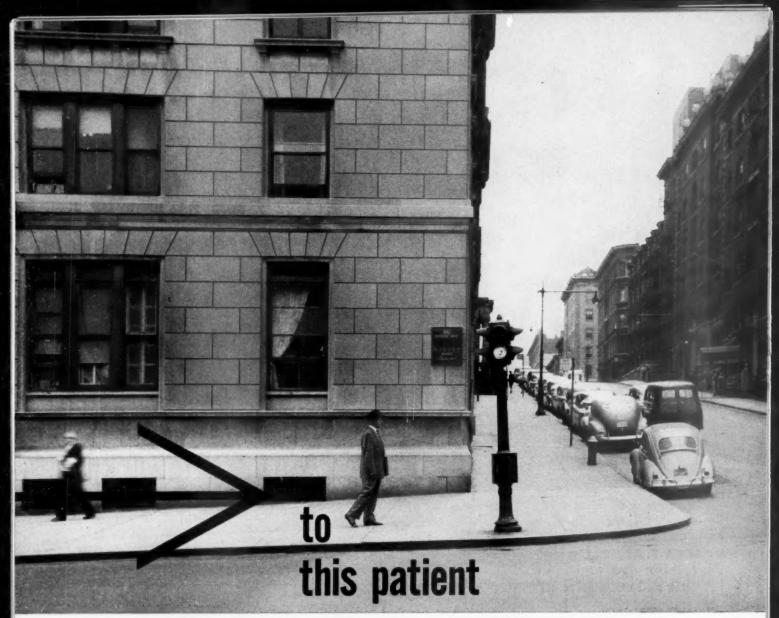
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makes the blocks so much shorter... he can walk many more of them in comfort

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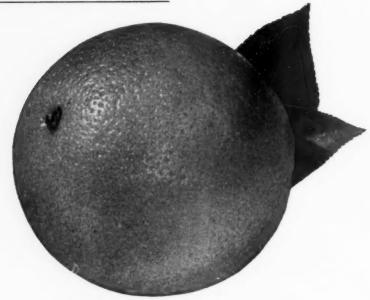
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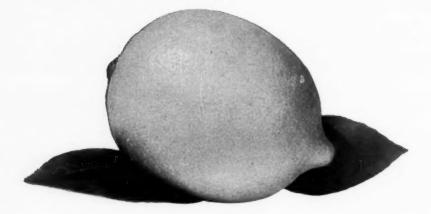
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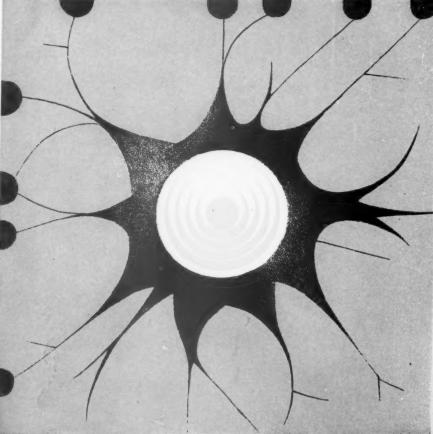
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References: 1. Ayd, E. J., Jr.: Bull. School Med. Univ. Maryland 44:29, 1959. 2. Azima, H., and Vispo, R. H.: A. M. A. Arch. Neurol. & Psychiat. 81:658, 1959. 3. Lehmann, H. E.; Cahn, C. H., and de Verteuil, R. L.: Canad. Psychiat. A. J. 3:155, 1958. 4. Mann, A. M., and MacPherson, A. S.: Canad. Psychiat. A. J. 4:38, 1959. 5. Sloane, R. B.; Habib, A., and Batt, U. E.: Canad. M. A. J. 80:540, 1959. 6. Straker, M.: Canad. M. A. J. 80:546, 1959. 7. Strauss, H.: New York J. Med. 59:2906, 1959.

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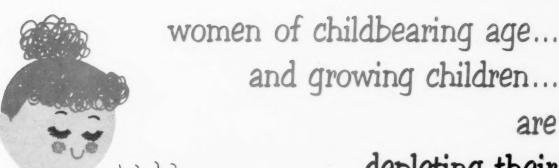
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- 1. Lehrer, H. W., et al.: Northwest Med. 75:1249, 1955.
- 2. Smith, Richard T.: New York Med. 8:16, 1952.

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 Cornely, D. A., and Ritter, J. A.: N-acetyl-p-aminophenol (Tylenol Elixir) as a Pediatric Antipyretic-Analgesic, J.A.M.A. 160:1219 (Apr. 7) 1956.

2. Mintz, A. A.: Management of the Febrile Child, J. Ky. Acad, Gen. Pract. 5:26 (Jan.) 1959.



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1. Babcock, G., Jr., and Packard, L. A.: Clin. Med. 6:985 (June) 1959.

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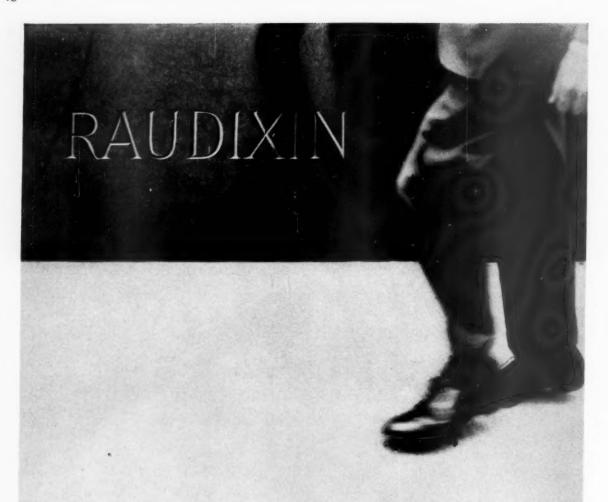
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Isordil significantly reduces the number, duration, and severity of anginal attacks, often when other long-acting coronary vasodilators fail. Exercise tolerance is increased, pain decreased, and the requirements for nitroglycerin either drastically curtailed or eliminated.

ISORDIL acts rapidly in comparison with other prophylactic agents, and patients usually experience benefits within 15 to 30 minutes. The effects of a single dose of ISORDIL persist for 4 to 5 hours. Thus, for most patients, convenient q.i.d. administration is highly satisfactory.

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Sherber,² summarizing his experience with Isordil, states it is "the most effective medication for the treatment of coronary insufficiency available today."



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Among 48 patients³ previously treated with other coronary vasodilators, chiefly pentaerythritol tetranitrate, ISORDIL was demonstrably superior in 37, equivalent in 9, and inferior in 2. Response of patients treated in all studies⁴ was 85% good, 7% fair, and 8% poor.

Markedly reduces number of anginal attacks:

Albert⁵ found that of 29 patients receiving ISORDIL, 25 responded well, 1 moderately well, and 1 not at all. Effectiveness could not be judged in 2 patients. For those who responded well, the frequency of anginal attacks was quickly reduced from a daily average of 5 to 1.2. Continued use of ISORDIL further reduced the frequency of attacks.

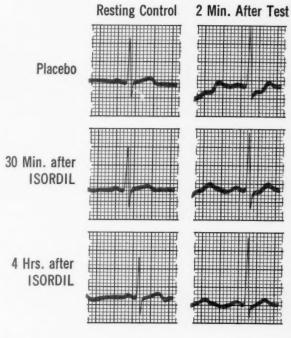
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Action: Following oral administration of ISORDIL, the effects of coronary vasodilatation are apparent within 15 to 30 minutes and persist for 4 to 5 hours.

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Dosage: ISORDIL is administered orally. Average dose is one tablet (10 mg.) taken one half hour before meals and at bedtime. Individualization of dosage may be necessary for optimum therapeutic effect; dosage may vary from 5 mg. to 20 mg. q.i.d.

Side Effects: Side effects are few, infrequent, and mild. Transitory headache, common to effective nitrate or nitrite therapy, has occurred. This usually responds to administration of acetylsalicylic acid, and disappears with continued therapy. When headache is persistent, reduction in dosage may be required.

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Supplied: Bottles of 100.

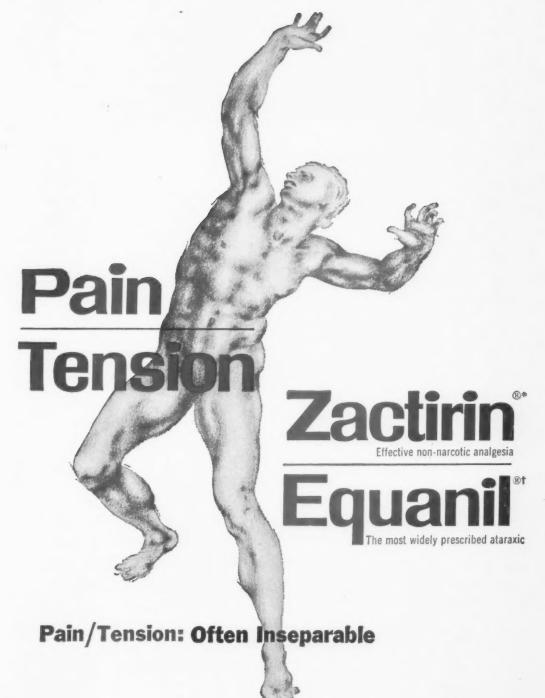
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1. Bartels, E. C., and Matossian, G. S.: Gout: Six-Year Follow-Up on Probenecid (BENEMID) Therapy, Arthritis and Rheumatism 2:193, June 1959.

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2. Lockie, L. M., and Talbott, J.: Does Your Patient Have Gout?, Scientific Exhibit, American Medical Association, New York City, June 3-7, 1957.

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3. Kron, K. M., Hermann, I. F., Smith, R. T., and Richards, J. C .: Which Rheumatic Disease?, Scientific Exhibit, American Medical Association, Atlantic City, June 8-12, 1959.

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toleration. Boger, W. P., and Gavin, J. J.,² Norristown, Pennsylvania – Side effects with DECLOMYCIN were minimal. When dosage was 0.5 to 1 Gm. daily in divided doses, only two of 82 patients exhibited nausea.

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gonococcal infection. Marmell, M., and Prigot, A.,⁴ New York, N. Y. – Of 63 cases of gonorrhea, 61 promptly responded after short courses of DECLO-MYCIN. Therapeutic effect was found equal to that of intramuscular penicillin.

bronchopulmonary infection. Perry, D. M.; Hall, G. A., and Kirby, W. M. M., Seattle, Washington – Of 30 cases of acute bacterial pneumonia, all were afebrile following two to 10 days of treatment with Declomycin. Results were good in 21.... All of six patients with acute bronchitis responded promptly.

pediatric Infection. Fujil, R.; Ichihashi, H.; Minamitani, M.; Konno, M., and Ishibashi, T., Tokyo, Japan – In 309 pediatric patients with various infections, Declo-MYCIN was effective in 75 per cent.

urogenital infection. Vineyard, J. P.; Hogan, J., and Sanford, J. P., Dallas, Texas – Clinical response in pyelonephritis correlated well with results of *in vitro* sensitivity tests, which showed some strains of A.



aerogenes, Proteus and Pseudomonas more susceptible to Declomycin Demethylchlortetracycline than to its analogues.

pneumonia. Duke, C. J.; Katz, S., and Donohoe, R. F., Washington, D. C.—Results were satisfactory in all but two of 32 cases of acute bacterial pneumonia, of which only 11 were uncomplicated. No side effects were observed.

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pustular dermatosis. Blau, S., and Kanof, N. B., New York, N. Y.—Results with DECLOMYCIN were excellent in both of two cases of impetigo, one of two cases of folliculitis, six of nine cases of furunculosis, all of three cases of acne rosacea and 26 of 45 cases of acne vulgaris. Overall, results were excellent or good in 85 per cent.

antibacterial spectrum. Finland, M.; Hirsch, H. A., and Kunin, C. M., Boston, Massachusetts—DECLOMYCIN Demethylchlortetracycline was found the most effective of the tetracycline analogues against two-thirds of 680 normally sensitive strains of 15 separate species.

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1. Russek, H.I.: Am. J. Cardiol. 3:547 (April) 1959.

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CATRON has displayed outstanding efficacy in depression, angina, and rheumatoid arthritis. But because of the nature of MAO inhibitor therapy, your attention is directed to the extensive and useful instructions prominently displayed in our literature on CATRON, and repeated below.

HOW TO USE CATRON:

CATRON is a monoamine oxidase (MAO) inhibitor useful in the treatment of depression and of other disorders indicated below. It is recommended for use in carefully selected cases and in those patients who have not responded to the milder drugs.

ADMINISTRATION AND DOSAGE:

Dosage of CATRON must be individualized according to each patient's response. The initial daily dose should not exceed 12 mg. and should be reduced as soon as the desired clinical effect is obtained. In severe depressions some clinicians desire rapid results and begin treatment with 24 mg. daily; this dosage should not be continued for more than a few days. A single daily dose in the morning is recommended. A continuous or interrupted schedule may be used, the latter during the maintenance period.

DEPRESSION (Endogenous, Reactive, Postpartum, Involutional, and Depression Secondary to Schizophrenic or Neurotic Reaction): initially, 12 mg. once daily for approximately 2 weeks, or less if improvement appears. Dosage is then reduced to 6 mg. daily. As improvement continues, maintenance dosage of 6 mg. every other day or 3 mg. daily often proves satisfactory. An interrupted dose schedule is recommended for long-term therapy.

ANGINA PECTORIS: 3 to 6 mg. daily in most cases. Relief of pain and elevation of mood may be dramatic. Victims of angina pectoris who respond in

this manner should be cautioned against overexertion induced by their sense of well-being.

RHEUMATOID ARTHRITIS (Adjunctive Therapy—in severely disabling forms, particularly when accompanied by depression): 9 to 12 mg. daily for 3 days, then 6 mg. daily, reducing further to 3 mg. daily on signs of improvement. If a conventional antiarthritic agent is used, lower doses of each are indicated.

CAUTION

Certain circumstances should be watched carefully when using CATRON.

DRUG POTENTIATION—The list of drugs which CATRON potentiates is not yet complete. Hence, caution should be exercised when combining CATRON with any other drugs such as tranquilizers, phenothiazines, the amphetamines, barbiturates, and hypotensive agents.

HYPOTENSIVE EFFECT—All normotensive patients receiving CATRON, but especially elderly patients, should be warned about the possibility of orthostatic hypotension during the initial period of higher dosage. In the few instances where this may occur, lowering of the dose will usually permit continuation of therapy.

VISUAL DISTURBANCES—A reversible red-green color defect has been reported in a few patients, chiefly hypertensive, on extended therapy with CATRON. Discontinue the drug if such changes

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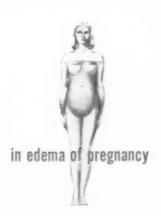
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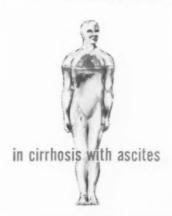
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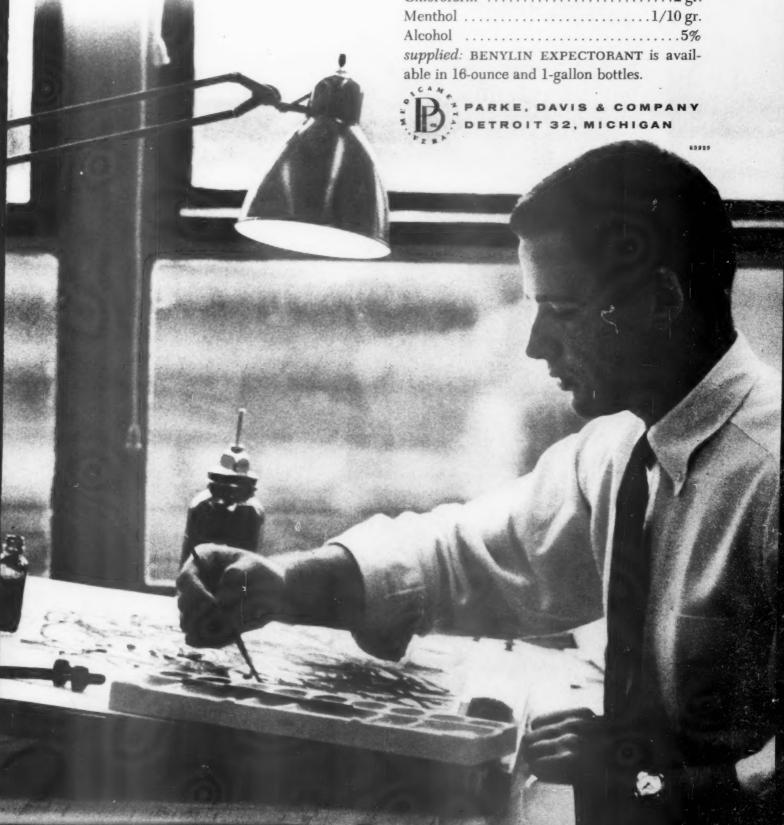
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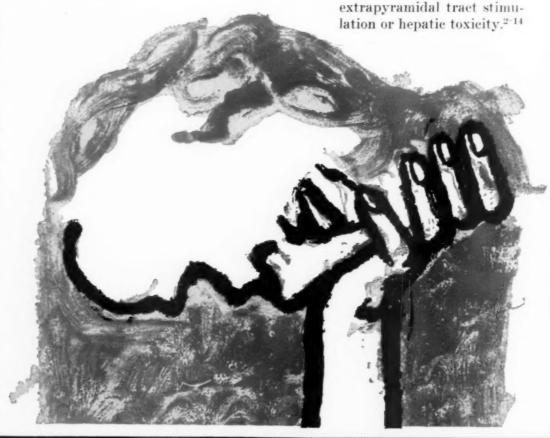


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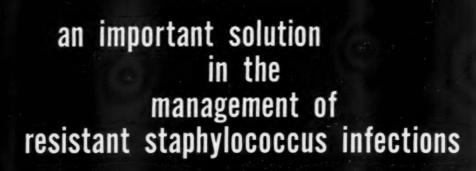
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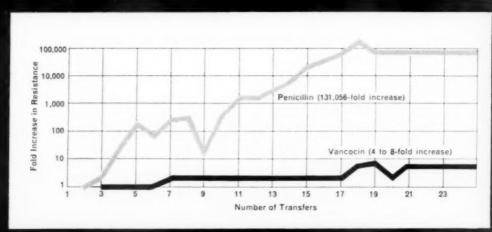
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No. 2

Editorial Renal Acidosis

The steady flow of hydrogen ions from their metabolic source to their excretion through the kidney is sometimes impeded by disease of that organ. This will come as no surprise to the practicing physician who is often called upon to treat the resultant metabolic acidosis. But as more has been learned of the intrarenal factors involved in the normal excretion of acid, the pathogenesis of renal acidosis has become an increasingly complex and intriguing problem.

This newer knowledge has been acquired to a large extent during the past decade under the leadership of such investigators as Pitts, Berliner, Gilman and many others who have produced extensive evidence that tubular exchanges of hydrogen ion are involved in the reabsorption of bicarbonate, in the acidification of other buffers (mainly phosphate) in the tubular urine, and in the tubular excretion of ammonium ion. These processes involve both donation and acceptance of hydrogen ions (or protons, to use the Bronsted terminology) and are conditioned by a variety of factors; these are presented schematically in Figure 1. Any inquiry into the effects of renal disease on the excretion of acid must take these processes and their conditioning factors into consideration.

It has long been known that progressive, generalized and destructive diseases of the kidney, such as chronic glomerulonephritis, pyelonephritis, nephrosclerosis and polycystic disease, interfere with the excretion of acid. In 1915 Palmer and Henderson and in 1926 van Slyke and co-workers showed that in patients with chronic glomerulonephritis the excretion of acid as ammonium ion was impaired to a greater extent than that as titratable acid, and the ability to acidify the urine, i.e., to lower pH, was relatively unimpaired. This pattern of renal malfunction in such uremic patients has been

confirmed by subsequent observers. On the other hand, a different type of disturbance of renal acid excretion has been recognized since Lightwood in 1935, and Butler, Wilson and Farber in 1936, described the first syndromes of specific tubular dysfunction with acidosis. In these non-azotemic acidotic patients, now reported in many different clinical settings, the principal defect appears to consist of inability to acidify the urine.

Thus for some time the acidosis of renal disease has been conceived to be of two main types, uremic acidosis and renal tubular acidosis, the former resulting primarily from glomerular failure and the latter from tubular failure. In uremic acidosis, according to this concept, progressive destruction and contraction of the kidney leads to reduction of the nephron population and hence of glomerular filtration; severely reduced filtration produces retention of phosphate and sulfate; these anions in turn "displace" extracellular bicarbonate and so result in metabolic acidosis. The diagnostic signs of uremic acidosis, therefore, are azotemia and hyperphosphatemia as well as depression of the serum bicarbonate. In renal tubular acidosis, on the other hand, specific tubular dysfunction in a "non-contracted" kidney interferes with the transfer and exchange of hydrogen ions into the tubular urine; the diagnostic hallmarks are hyperchloremic extracellular acidosis, absence of azotemia and the presence of a relatively alkaline

This concept of renal acidosis has recently been challenged in two stimulating papers by Schwartz, Relman and co-workers [1,2]. First, these authors point out that the acidosis of the uremic patient is more correctly stated to be due to the retention of metabolically-produced hydrogen ion than to accumulation of the anions,

phosphate and sulfate. Secondly, they suggest that since essentially all the hydrogen ion excreted is transferred into the urine through the cells of the renal tubule, all acidoses of renal origin must be renal tubular acidosis. In support of this concept Schwartz, Hall, Hays and Relman [2] have presented data that indicate that some (but not all) of their uremic patients failed to conserve bicarbonate under experimental conditions of bicarbonate loading.

In part, the difficulty is semantic and as such will not be belabored here again [3]. Metabolic production and retention of hydrogen ion inevitably is associated with reduction in the capacity of the buffer systems in the body fluids; this, as quantified by the fall in concentration of total buffer anions or buffer base, is merely the other side of the coin. In part, however, the difficulty is in interpretation and so warrants

careful analysis and experimentation.

Retention by the uremic patient of the anions, phosphate and sulfate, derived along with hydrogen ions from the dietary and metabolic pool, will not lead per se to extracellular acidosis if the retention takes place with equivalent numbers of sodium ions while the hydrogen ions are excreted. But other factors regulating body fluid osmolality and volume supervene to cause excretion of the sodium. Since this cannot occur with sulfate or phosphate, it must with chloride or bicarbonate. If the sodium is excreted with chloride (and this is probably the mechanism of the hypochloremia of the uremic patient who does not vomit), extracellular bicarbonate and total buffer anion (equivalent to buffer base) is unchanged and the original metabolic hydrogen, formed as sulfuric acid and buffered by reaction with sodium bicarbonate, is excreted through the lungs as carbon dioxide and water. If sodium is excreted with bicarbonate, extracellular buffer anion (or buffer base) is decreased; in this case the metabolic hydrogen is retained along with the phosphate and sulfate and a state of acidosis ensues. But the real crux of the matter is this: granting that the final common pathway of the hydrogen is through the tubular cell, what are the factors limiting its excretion in the contracted kidney? Is it the non-availability of proton acceptors (phosphate as limited by reduced filtration and/ or ammonia as limited by defective tubular production) or is it deficient tubular proton donation due to tubular damage?

There is a considerable body of evidence that

tubular functions other than hydrogen ion transfer, maximal paraminohippurate transport for instance, are damaged in progressive and contractive renal disease. Likewise, the plasma bicarbonate level may fall before the levels of phosphate, creatinine or non-protein nitrogen rise to any marked degree. These observations support the concept that tubular damage, parallel to glomerular damage, is a factor in the impairment of the excretion of acid in this type of renal disease. But in the uremic patient with acidosis the question appears to be unsettled as to whether the primary factor in its production is defective tubular proton donation or deficiency of proton acceptors. To me, the latter appears to be the most likely probability but further experimentation is clearly in order.

Unanswered questions also lurk amid the pathogenic complexities of the acidotic renal patient without azotemia, the patient with the "non-contracted" kidney. As the term is now generally used this is renal tubular acidosis. Such a patient fails to donate protons or hydrogen ions from renal tubular cells to acceptor substances in the tubular urine, mainly bicarbonate, phosphate and ammonia. Is this failure of proton donation due to the breakdown of a single mechanism? That such is the case seems improbable since quite a variety of factors condition the tubular processes of proton donation, as indicated in Figure 1. Of these factors the ones most likely to be involved in the tubular failure of proton donation in this disease are: (1) the facilitation of hydrogen ion availability by carbonic anhydrase and (2) the supply of energy for active transport by the Krebs tricarboxylic cycle. Interference with either of these processes leads to a decreased rate of excretion of acid, as is shown experimentally by inhibition of carbonic anhydrase with acetazolamide and by blocking of the Krebs cycle with maleic acid [4,5]. Both of these factors therefore require careful consideration in any study of the pathogenesis and, indeed, of the etiology of renal tubular acidosis.

Primary failure of mass donation of protons against a low concentration gradient has been ruled out in many patients in whom the excretion of titratable acid has increased when urinary phosphate acceptors have been greatly multiplied by the administration of phosphate; it is made unlikely by the experimental demonstration that the limit to this type of augmentation is manyfold the normal excretion rate of

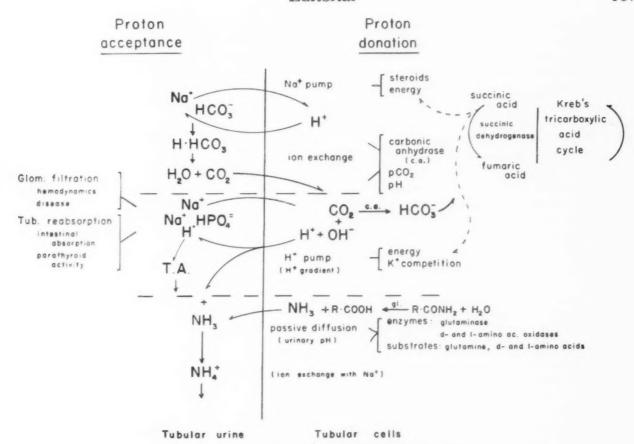


Fig. 1. Factors in the renal excretion of hydrogen ion.

hydrogen ion. On the other hand, most of the patients studied have been reported to excrete relatively alkaline urines containing bicarbonate in the presence of frank systemic acidosis. These observations indicate the pathogenic defect to be a failure of the hydrogen ion "pump" to move the ion against the concentration gradient. The cause of such a defect could well lie in an inadequate supply of energy from the Krebs cycle or in deficient activity of the enzyme, carbonic anhydrase; these pathogenic factors, however, remain to be established.

But does this characterization of renal tubular acidosis account for all the renal acidotic patients with "non-contracted" kidneys? In my opinion it does not. Primary deficiency of proton acceptors in the tubular urine does not depend on failure of glomerular filtration alone. (Fig. 1.) The amount of phosphate excreted is a function of the amount reabsorbed as well as of the amount filtered. An inadequate intake of phosphate (vitamin D resistance, steatorrhea), or decreased parathyroid activity might be factors that increase the tubular reabsorption

and diminish the excretion of phosphate acceptor of hydrogen ion. Specific failure of the tubular production of the proton acceptor ammonia (as opposed to inhibition of transfer by the alkalinity of the tubular urine) also might lead to inadequate excretion of hydrogen ion. That both of these types of proton acceptor deficiency may occur in the acidotic patient with the "non-contracted" kidney is suggested by the experience of our group [6,7]. Under these circumstances it would appear that either the definition of the term renal tubular acidosis should be broadened or some new diagnostic categories need to be defined.

There are a number of other difficulties that beset the physiologic diagnosis of renal tubular acidosis. One of these is the precise separation of glomerular failure and tubular failure; even in the conventionally accepted type, the non-azotemic acidotic patient with a relatively alkaline urine, such separation is not always clear-cut. The majority of patients described to date show some depression of the filtration rate and apparently a number of these patients, especially those with associated nephrocalcinosis

and nephrolithiasis, may undergo progressive renal damage with the onset of uremia. Another difficulty lies in the balance between the several intrarenal mechanisms involved in the excretion of hydrogen ions. Wrong and Davies [8] in their recent excellent analysis of the excretion of acid in renal disease describe two cases in which the defect in excretion of titratable acid is counterbalanced to the point of preventing acidosis by an excessive excretion of ammonium ions; these cases they label *incomplete renal tubular acidosis*. Such observations exemplify the fact that a normal rate of excretion of hydrogen ions may exist in the presence of a defect in one of the renal acidification mechanisms.

Indeed, inadequate recognition has been given to the possible existence of minimal, subclinical or latent cases of renal acidosis. This possibility is rendered all the more likely by the demonstration of a familial factor in some cases of typical renal tubular acidosis; genetic impairment in heterozygotes would not be expected necessarily to show clinical manifestations. Yet detection of such impairment of the kidney's ability to excrete hydrogen ion is essential to elucidation of the role of genetic factors in the etiology of the disease. Thus there may be some persons without abnormal retention of hydrogen ions (acidosis) who can excrete the normal daily amounts of hydrogen ion metabolically produced but who cannot dispose of unusual increments in this acid load. And undoubtedly the patients with overt acidosis most of the time are able to put out the normal daily hydrogen ion load but at the same time are unable to excrete additional amounts of the ion metabolically produced or already retained. Under conditions of a high acid load both types of patients should exhibit a low renal "clearance" of hydrogen ion, i.e., a low ratio of hydrogen ion excreted to the amount

retained in the body fluids. If such a ratio could be quantified, it should prove to be a useful diagnostic tool.

Perhaps enough has been said to indicate the complexities of the problem of acidosis of renal origin. Clearly, a variety of vicissitudes awaits the hydrogen ion in its journey through the diseased nephron. Clarification of these complexities in terms of pathogenesis, etiology and diagnosis presents a continuing challenge to the physiologist, to the biochemist, to the geneticist and, most of all, to the inquiring physician.

J. Russell Elkinton, M.D.
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University of Pennsylvania School of Medicine,
Philadelphia, Pennsylvania

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The Diagnosis and Treatment of Renal Hypertension*

With Special Reference to a Case of Hypertension Due to Stenosis of Both Renal Arteries

E. R. YENDT, M.D., W. K. KERR, M.D., D. R. WILSON, M.D. and Z. F. JAWORSKI, M.D. †

Toronto, Canada

CINCE Goldblatt et al. [1] reported that hypertension could be produced in the dog by partial constriction of the renal arteries clinicians have been searching for the human counterpart of the Goldblatt experiment in the hope of finding cases of hypertension which could be alleviated by the removal of one diseased kidney. Many hypertensive patients with unilateral renal disease of various sorts were subjected to nephrectomy but, although there were sporadic reports of success, the percentage of cures was small: in published cases less than 20 per cent [2]. Because of this disappointing experience clinical interest in this field tended to wane and in some centres the removal of a kidney in an attempt to cure hypertension, rather than for established urological indications, was looked upon with disfavour.

During the past six years there has been a considerable revival of interest in this subject. In 1953 Howard and his associates [3,4] presented evidence that, when hypertension was associated with a lesion which interfered with the arterial blood flow to a kidney, i.e., when the true clinical counterpart of Goldblatt's experimental conditions obtained, there was an excellent chance of its alleviation by nephrectomy. Howard and his co-workers also pointed out that routine methods of urological investigation, such as intravenous and retrograde pyelography, often failed to detect such cases and they demonstrated the value of differential renal function studies and abdominal aortography as

diagnostic procedures. Cases of hypertension due to interference with the arterial blood supply to the kidney are now being reported with increasing frequency [5,6] and the results of surgical treatment in such cases have been generally good.

Poutasse et al. [7] recently reported cases of hypertension resulting from stenosis of both renal arteries. In one patient surgical correction of the arterial lesions by excision of the strictures and insertion of arterial homografts was successful in alleviating the hypertension.

It is the purpose of this paper to discuss the diagnosis and treatment of hypertension, based on experience gained at the Toronto General Hospital during the years 1954 to 1958, and to report in detail another case of hypertension due to stenosis of both renal arteries.

CASE REPORT

Mrs. M. T. (T.G.H. No. E15697), a twenty-seven year old housewife, was referred to the Toronto General Hospital on June 30, 1957, by Dr. M. F. Clarkson of Peterborough, Ontario, as a case of renal hypertension.

Her past history was non-contributory. She had measles, mumps and chickenpox as a child. There was no history of severe injury or of operation, or of unexplained abdominal pain. There was no family history of hypertension.

The patient had always had excellent health. She had had two uncomplicated pregnancies, both terminating in normal deliveries in February 1954 and in September 1955. Numerous blood pressure readings

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† R. Samuel McLaughlin Travelling Fellow.

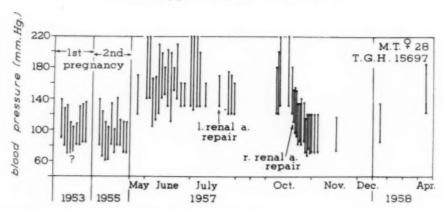


Fig. 1. Hypertension due to bilateral stenosis of the renal arteries. Patient M. T. Blood pressure chart.

taken during and after both pregnancies were normal. She remained well until May 1957 when, during the third month of her third pregnancy, she had a spontaneous abortion. At that time her blood pressure was 170/120 mm. Hg. Thereafter, numerous blood pressure recordings showed that the hypertension was persistent and of fairly marked degree. (Fig. 1.) However, she continued to enjoy reasonably good health, her only complaint being mild fatigue. There were no symptoms of cardiac decompensation and no complaints referable to the urinary system.

She was admitted to the Peterborough Civic Hospital on June 11, 1957. While there the patient continued to have moderately severe hypertension even with mild sedation. The blood pressure varied between 160 and 210 systolic, and 110 and 150 diastolic; most diastolic readings were over 120. (Fig. 1.) During the course of the investigations an intravenous pyelogram was obtained and reported as normal. There was prompt excretion of dye in good concentration by both kidneys, and the collecting systems appeared

normal. (Fig. 2.) Cystoscopy and ureteral catheterization were performed; urine was collected from the two kidneys simultaneously. The results are shown in Table I. Because of the reduction in volume and sodium concentration of the urine obtained from the left kidney a renal cause for the hypertension was suspected, and the patient was transferred to the Toronto General Hospital on June 30, 1957, for further investigation.

On examination the patient was a healthy looking, well developed, well nourished young woman, measuring 5 feet 6 inches in height and weighing 127 pounds. She was intelligent and highly cooperative. Pulse, temperature and respirations were normal. The blood pressure was 200/120 mm. Hg in the right arm. The pulse was weaker at the left wrist than at the right, and systolic pressures recorded in the left arm were persistently 10 to 20 mm. Hg lower than in the right. There was moderate narrowing of the retinal arterioles without segmental spasm; there were no haemorrhages, exudates or papilloedema.



Fig. 2. Patient M. T. Normal intravenous pyelogram.

Table 1
PATIENT M. T. DIFFERENTIAL SODIUM EXCRETION

		Urine from										
Date	Blood Pressure	Righ	nt Kidney	Left Kidney								
Date	(mm. Hg)	Vol- ume (ml.)	Sodium Concen- tration (mEq./L.)	Vol- ume (ml.)	Sodium Concen- tration (mEq./L.)							
June 1957 (before operation)	200/135	20	38	10	3.4							
left renal artery re- paired)	220/135	3.5	87	53	219							
(after right renal artery repaired)	135/85	?	120	?	124							
November 1958 (after recurrence of hypertension)	180/120	22	19	63	37							



Fig. 3. Patient M. T. Aortogram. The left renal artery is constricted near its origin. Only a short stump of the right main renal artery is filled. An aberrant artery supplies the lower pole of the right kidney.

The chest was clear. The cardiac beat was forceful; the point of maximal impulse was in the fifth left intercostal space, 10 cm. to the left of the midline. The cardiac rhythm was regular and there were no murmurs. The aortic second sound was increased in intensity. On examination of the abdomen nothing abnormal was found; an abdominal bruit was not listened for. The dorsalis pedis and posterior tibial pulsations were strong and equal. The blood pressure in the leg was 220/130 mm. Hg.

Haemoglobin, red blood count and white blood count were all within normal limits. The serum sodium was 140 mEq./L.; serum potassium, 3.5 mEq./L.; serum chloride, 105 mEq./L.; and serum CO₂ combining power, 30.8 mM/L. The blood nonprotein nitrogen was 35 mg./100 ml. The urine contained a trace of albumin but was negative for blood and sugar; there were no cells or casts in the spun sediment. The maximum specific gravity of the urine, after fluid restriction for eighteen hours, was 1.020. Phenolsulphonphthalein excretion was 30 per cent in fifteen minutes and 70 per cent in two hours. Creatinine clearance, 132 ml./minute; p-aminohippurate (PAH) clearance 760 ml/minute; TmpAH 69 mg./minute (not corrected for surface area). The electrocardiogram was normal. A regitine test was negative. A chest roentgenogram disclosed no abnormalities.

Catheterization of the ureters and simultaneous collection of urine from the two kidneys was repeated and essentially the results were the same as on the previous study made at Peterborough, viz: a reduction of volume and sodium concentration of the urine obtained from the left kidney as compared with urine collected at the same time from the right kidney. Since these results suggested inequality of the arterial blood supply to the kidneys, abdominal aortography

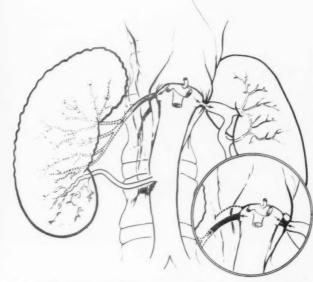


Fig. 4. Patient M. T. Diagram illustrating the anatomic defects encountered at operation. The left renal artery was constricted near its origin. The right main renal artery was completely occluded for a distance of about 3 cm.; the upper two-thirds of the kidney was flabby. An aberrant artery supplied the lower pole of the right kidney which appeared normal. Note the impingement of the tendinous crura of the diaphragm upon the renal arteries.

was performed. This procedure demonstrated stenosis of both renal arteries. There was marked segmental narrowing of the left renal artery near its origin from the aorta. The right main renal artery could not be visualized, although there was a short stump which was thought to indicate its probable point of origin from the aorta. An aberrant artery supplied the lower pole of the right kidney. (Fig. 3.) The anatomic defects are depicted in Figure 4.

On July 19, 1957, the left renal artery was repaired via a lumbar incision through the twelfth rib. Careful dissection around the renal pedicle was necessitated by the numerous small collateral vessels about the renal pelvis. Dense adhesions were encountered around the origin of the left renal artery. It was eventually found necessary to divide the left crus of the diaphragm which impinged on the origin of the renal artery. When sufficient aorta had been exposed it was possible to place a curved arterial clamp longitudinally on the aorta, excluding the origin of the renal artery from the circulation without obstructing the aorta. Thickening of the renal artery was palpable just beyond its origin and a thrill could be felt. The vessel was now resected piecemeal until normal artery was obtained distally. Proximally it was necessary to resect the artery flush with the aorta; a normal arterial wall was still not obtained. It was possible, however, to suture the arterial stump to the side of the aorta with continuous arterial suture. The wound was closed in layers without drainage. The operative pro-

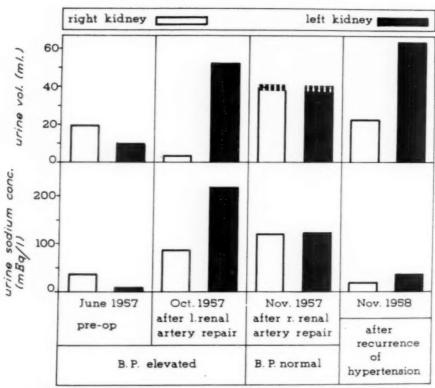


Fig. 5. Differential renal function studies. Diagram showing urine volume and sodium concentration in patient M. T. with hypertension due to stenosis of both renal arteries.

cedure took four and a half hours during which the blood supply to the left kidney was occluded for forty-five minutes. In order to protect this kidney from the effects of complete ischaemia, local hypothermia was applied. Upon clamping the arterial supply, coils of penrose tubing containing ice cold sterile normal saline solution were wrapped around the kidney for five minutes, lowering the temperature in the centre of the kidney to 27°c.

The patient withstood the procedure well and the postoperative course was uncomplicated. A cystoscopic examination was performed on the first day after operation: after the injection of indigo carmine, dye appeared at both ureteral orifices in five minutes. An intravenous pyelogram taken two weeks after operation showed prompt excretion of dye in good concentration by both kidneys. During the postoperative period the patient remained hypertensive and, when discharged from the hospital on August 3, 1957, the blood pressure in the left arm was still 160/124 mm. Hg.

Following discharge from the hospital the patient remained well except for intermittent discomfort over the precordium. The exact nature of this discomfort was undetermined. The blood pressure was checked frequently and remained elevated. (Fig. 1.) On October 6, 1957, she was readmitted to hospital for surgical repair of the right main renal artery. No changes were found on physical examination at this

time. The blood pressure was 195/120 mm. Hg in the right arm and 170/125 in the left arm. A voided specimen of urine had a specific gravity of 1.019; it contained a faint trace of albumin and there were no cells or casts in the spun sediment. Routine haematologic studies were again normal. The serum sodium was 136 mEq./L.; serum potassium, 3.1 mEq./L.; serum chlorides, 103 mEq./L.; and the CO2 combining power, 33.4 mM/L. The blood non-protein nitrogen was 34 mg./100 ml. On October 9 differential urine volume and sodium excretion studies showed a complete reversal to those obtained prior to repair of the left renal artery. The volume of urine obtained from the left kidney was 53 ml. and, although there was a steady slow drip of urine from the right kidney, only 3.5 ml. of urine was obtained from this kidney over the same period of time. There was no leakage of urine into the bladder. The sodium concentration of the urine from the left kidney was 219 mEq./L., whereas that from the right kidney was 87 mEq./L. Indigo carmine dye appeared from the left catheter in two minutes and from the right catheter in eight minutes. (Table 1 and Fig. 5.)

On October 17, 1957, the right renal artery was repaired. The right kidney was exposed by a thoracoabdominal incision through the bed of the ninth rib. The diaphragm was divided along its costal attachment. Numerous collateral vessels along the ureter and renal pelvis were again encountered. The kidney

and its pedicle were turned forward with the vena cava in order to expose the origin of this renal artery. Again the crus of the diaphragm was found to impinge on the first centimeter of renal artery. In the dissection of dense fibrous adhesions here, the cisterna chyli was opened in two places and had to be repaired. The crus of the diaphragm had to be divided for over an inch before the origin of the renal artery could be exposed. As well as the main renal artery there was an aberrant artery supplying the lower onethird of the kidney, as judged by a line of demarcation seen on the surface of the kidney. A curved arterial clamp was applied to the aorta, excluding the origin of the main renal artery; the stenosed portion of the renal artery was excised in segments. It was found to be completely occluded from its origin for a distance of about 3 cm. to within a few millimeters of its bifurcation in the renal hilus. An end-to-side anastomosis was then carried out between the stump of the renal artery and the side wall of the aorta. Diaphragm, chest and abdomen were then closed with drains in both the pleural and abdominal cavities. The operative procedure took six hours. As this kidney was not subjected to additional ischaemia, local hypothermia was not used. The upper twothirds of the kidney, which had been ischaemic and flabby before the restoration of its blood supply, became distended and tense and the previous line of demarcation between ischaemic and normal kidney

Postoperatively, the patient made a rapid recovery, the only complication being a wound infection due to Staphylococcus aureus. On her return from the operating room her blood pressure was 140/90 mm. Hg. On the first postoperative day the highest blood pressure recorded was 150/110 and by the second day all readings were below 150/90 mm. Hg. From then until her discharge from hospital one month after the operation her blood pressure remained normal, the usual reading being 120/75 in the right arm and 90/70 in the left arm. (Fig. 1.) Four weeks after operation differential sodium excretion studies were repeated. Urine sodium concentrations were now equal on the two sides. On this occasion there was a steady drip of urine from both ureteral catheters, suggesting that urine was now being excreted by the two kidneys in fairly equal amounts. Unfortunately, however, leakage of urine around the catheters into the bladder prevented accurate determination of urine volume. (Table 1 and Fig. 5.) On January 17, 1958, her blood pressure was 135/85 in the right arm and 115/85 in the left arm. The urine had a specific gravity of 1.030; it contained no albumin, blood, sugar or pus.

However, in the spring of 1958 it was noted that the patient was again hypertensive. At first the hypertension was mild and, after ten to fifteen minutes' rest in the recumbent position, normal blood pressure levels could be obtained. Later the hypertension

TABLE II PATIENT M. T. RENAL FUNCTION STUDIES AFTER RECURRENCE OF HYPERTENSION, NOVEMBER 1958

Renal Function Studies	Right Kidney	Left Kidney
Volume (ml.)	22	63
Specific gravity	1.004	1
pH	6.3	6.65
Creatinine (mg. %)	1.5	0.6
Ammonia nitrogen (mg. %)	18.5	1.9
Sodium (mEq./L.)	19	36.9
Potassium (mEq./L.)	5.5	4
Calcium (mg. %)	1.58	2.16
Magnesium (mg. %)	1.12	0.84
Chloride (mEq./L.)	19.4	30.4
Inorganic phosphorus (mg. %)	5.5	5

became sustained. In July 1958, the patient was feeling quite well. On examination the blood pressure in the right arm was 180/120 and in the left arm 160/140; after fifteen minutes of rest in the recumbent position the blood pressure in the right arm was 160/105. A loud systolic bruit could be heard over the upper portion of the abdomen. It was of maximum intensity in the upper part of the epigastrium in the midline and just to the right of the midline; it could also be heard in the right costovertebral angle. A loud systolic bruit could also be heard in the neck; it was loudest in the sternal notch and along the course of

the right carotid artery.

On November 2, 1958, the patient was readmitted to the hospital for further investigation. During this admission, the blood pressure averaged 170/120 mm. Hg. On examination there was moderate narrowing of the retinal arterioles but no evidence of retinal haemorrhages, exudates or papilloedema. The cardiac impulse was forceful, the point of maximum impulse being in the fifth intercostal space, 10.5 cm. to the left of the midline. There were no cardiac murmurs. The previously described bruits in the abdomen and neck were unchanged. Chest x-ray examination showed no evidence of cardiac enlargement, and the electrocardiogram was normal. Differential renal function studies were repeated. There was a significant decrease in the volume and sodium concentration of urine collected from the right kidney. (Table 1 and Fig. 5.) However, the disparity in volume of urine obtained from the two kidneys was much less than immediately before the second operation, and the relatively large amount of urine obtained from the affected (right) kidney allowed much more detailed comparison to be made of the electrolyte excretion by the two kidneys than had been possible previously. (Table II.)

In view of the equal function of the two kidneys with regard to urine sodium concentration during the normotensive period following the second operation, the findings of the most recent studies would suggest that the right renal artery is again stenosed; this is also suggested by the nature of the abdominal bruit which is louder on the right side of the abdomen and also audible in the right, but not in the left, costovertebral angle.

The Nature of the Arterial Lesions

We are grateful to Dr. J. D. Hamilton, Professor of Pathology, University of Toronto, for reviewing the excised segments of the renal arteries in this case. His

report is as follows:

"Both renal arteries were stenosed near their origin by fibrous intimal thickening, but this did not resemble an atheromatous plaque and was only one part of an extensive morphologic change involving all coats of the arterial wall.

"The most striking feature was the alteration in elastic tissue. The internal elastic lamina was in some areas straight and flat, sharply defined and lacking the undulating character it usually has in tissue sections. This changed in other areas into a folded, broadened band terminating abruptly and leaving a gap in the lamina. Elsewhere in its circumference there were deficiencies of varying extent, with some fragments of elastica having a blurred, smudgy appearance.

"The external elastica lamina showed equally prominent fragmentation, retraction and degeneration with splitting, or reduplication, into several layers. One did not see, in association with the altered elastica, basophilic change in ground substance, although this was evident in a few small areas in the

media.

"As stated, there was a thick layer of fibrous connective tissue inside the internal elastic lamina. In longitudinal sections of the vessels, this tissue was cellular, contained small blood channels and appeared to stream though the gaps in the elastica, to separate the media into inner and outer layers and, in some sections, extended through the external elastic lamina to fade away finally in the adventitia. There was therefore a tremendous thickening of the vessel wall in these areas, thickening due to the fibrous tissue in intima, splitting the media and extending into adventitia. The lumen was narrowed to a variable extent and, where the stenosis was most marked, the tissue in the lumen had the appearance of organised and re-canalised thrombus, with irregular anastomosing channels separated by connective tissue and showing in places the development of smooth muscle fibres. No inflammatory cells were noted in any layers of the vessel, other than a few lymphocytes in the adventitia.

"One is led to the opinion, from the association of striking degeneration of elastica, some basophilic degeneration of media and vascular fibrous tissue extending from the intima through and into the media and adventitia, that in the pathogenesis of the stenosis of these renal arteries the initial event may have been degeneration of elastica, and possibly muscle in the media, with rupture and haemorrhage into the wall in the manner of a dissecting aneurysm with subsequent organization of the haematoma. The pathologic modifications of the media do not, however, resemble Erdheim's medial degeneration very closely, but this may be related to the difference in structure of the vessel involved.

"In support of these interpretations of the renal artery lesions are the clinical observations of other vascular abnormalities, including inequality of blood pressure in the arms and a loud bruit heard in the neck at the base of the right common carotid artery.

"As mentioned, there were no inflammatory cells seen in the renal artery lesions and nothing to suggest that the changes are the result of an arteritis. They appear to be primarily degenerative and reparative and, although these features resemble those of Erdheim's medial degeneration, similar changes have not been described in renal or other major branches of the aorta in dissecting aneurysm."

(Dr. Hamilton has also examined the renal arteries in our other two cases of bilateral renal artery stenosis (Cases 10 and 16, Table v) and is of the opinion that the pathologic process is the same in all three cases.)

We think it advisable to observe the course of this patient before aortographic studies are repeated or further surgery is considered. In the meantime she is being treated with hypotensive drugs. At the present time she receives 250 mg. of chlorothiazide twice daily, 25 mg. of hydralazine four times a day and 0.2 mg. of reserpine daily; on this regimen her blood pressure is usually 150/95 mm. Hg.

DIAGNOSIS OF RENAL HYPERTENSION

The history of this patient (Mrs. M. T.) led to the suspicion that her hypertension was not of the essential variety. She was only twenty-seven years old, and less than two years prior to the finding of a severe degree of hypertension she was known to have had normal blood pressure. Although the intravenous pyelogram was normal, differential renal function studies strongly suggested that the hypertension was secondary to renal arterial disease. The nature of the arterial abnormality was elucidated by abdominal aortography.

The plan of investigation used in this patient and the following remarks concerning the diagnosis of renal hypertension are based on experience with twenty patients studied at the Toronto General Hospital during the years 1954 through 1958. This group includes all patients who have undergone either nephrectomy or renal artery surgery in the hope of alleviating hypertension

AMERICAN JOURNAL OF MEDICINE

during this period of time. The underlying disease in twenty cases is listed in Table III. It is of interest that in thirteen patients there was evidence of renal arterial insufficiency; three patients had stenosis of both renal arteries. During the same period the total number of patients investigated for possible renal lesions was 125.

The Clinical Picture. Hypertension is a common disorder but the number of cases secondary to renal disease is small. It is difficult to set forth rigid criteria which will ensure that no patient with renal hypertension will remain undiagnosed, and which will at the same time prevent much unnecessary, fruitless and potentially dangerous investigation. At present we consider the following criteria of value in making such a decision.

It has been reported from several clinics, and it has also been our experience, that patients with renal hypertension are likely to fall into one of the following groups: (1) patients in whom the hypertension has been of recent onset and rapidly progressive, with the early development of symptoms; (2) elderly patients in whom malignant hypertension develops suddenly; (3) young patients in whom no other cause for hypertension can be demonstrated; (4) patients of any age with known essential hypertension in whom symptoms abruptly become more severe; (5) patients whose history suggests the possibility of a renal vascular accident, i.e., a history of peripheral arterial emboli, of renal trauma, of some surgical procedure such as the ligation of an aberrant renal artery, or of an unexplained attack of pain in the loin or abdomen which might have accompanied renal infarction.

The possibility of renal hypertension in patients falling into any of the foregoing categories should be considered carefully with a view to the institution of appropriate investigation. However, a few patients with renal hypertension do not fall within these categories. Occasionally the hypertension may be of many years' duration without evidence of an abrupt exacerbation of symptoms at any time. One of our patients was known to have had hypertension for at least ten years (Case 13, Table v); her only symptom was mild exertional dyspnoea which had been present for five years. It is our view that the possibility of an underlying renal basis should be considered in any patient who has hypertension which is severe or associated with cardiac, renal or neurologic sequelae. For the most part, renal hypertension is not mild or asympto-

Table III
UNDERLYING DISEASE IN TWENTY CASES OF RENAL
HYPERTENSION
(Toronto General Hospital, 1954–1958)

Underlying Disease	No. of Cases
Renal artery lesion (13 cases)	
Stenosis or occlusion of one renal artery Stenosis of both renal arteries	3
Renal infarcts	2
Mitral stenosis, postcommissurotomy Infarction secondary to aneurysm of renal	1
artery	1
Multiple cholesterol emboli	1
Probable renal artery lesion	1
"Unilateral" pyelonephritis	2
Stenosis of one ureter	2
Perinephric fibrosis	1
Postradiation nephritis	1
Staghorn calculus, hydronephrosis, pyelonephritis	1

matic, and bedrest in a hospital usually does not produce the rapid decline in blood pressure to normal or near normal levels which is so frequently seen in patients with essential hypertension. It is not our policy at present to encourage special investigation in patients whose blood pressure falls quickly with rest. In our experience, the response or lack of response to the administration of hypotensive drugs has been of no value in differentiating renal and essential hypertension.

Standard Tests of Renal Function. In the investigation of a patient with suspected renal hypertension the usual tests of renal function are of little diagnostic value. As in the patient herein described, all the routine tests, including urinalysis, the measurement of concentrating power, phenolsulphonphthalein excretion and the blood non-protein nitrogen, may be normal or near normal; furthermore, any impairment of renal function detected by such tests might occur in hypertension from any cause. The inulin clearance, PAH clearance* and TmPAH were normal in the case described; had changes been detected, they would have been nonspecific. If these tests are used to study the function of each kidney separately following ureteral catheterization one might obtain evidence of some discrepancy between the function of the two kidneys

^{* 760} ml. per minute. It is of considerable interest that measurement of renal blood flow gave normal results despite the marked stenosis of both renal arteries.

DIFFERENTIAL SODIUM EXCRETION STUDIES IN TWENTY CASES OF RENAL HYPERTENSION

Findings	No. of Cases
Unilateral disease (17 cases)	
No urine from affected kidney	8
Reduced urine volume	9
Sodium concentration decreased	6*
Sodium concentration equal	1†
Sodium concentration increased	1†
Sodium concentration variable	1‡
Bilateral renal artery stenosis	3
All had marked inequality of urine volume and sodium concentration	

* All these patients had renal artery lesions.

† These patients had unilateral pyelonephritis.

‡ This patient had mitral stenosis and renal infarcts.

but no specific information which would aid in differentiating the "Goldblatt kidney" and unilateral renal disease of other causes. Standard tests of renal function are of value, however, in assessing the over-all renal function of a patient with hypertension.

Intravenous Pyelography. The inadequacy of intravenous urography as a diagnostic tool in renal hypertension is now well recognized [4,6,8]. In six of our twenty patients, including the case reported in detail, the intravenous pyelogram was normal. In other cases the affected kidney was reduced in size but still able to concentrate dye quite well. At times there was complete non-function of the involved kidney; in such cases the retrograde pyelogram may appear

Differential Sodium Excretion Studies. Since the history, urinary findings, usual renal function tests and even intravenous pyelography may be insufficient to establish a diagnosis of renal hypertension, cystoscopy and ureteral catheterization should be performed for urine volume and sodium concentration studies.

This differential renal function test is based on the experimental work of White [9,10] who found, in the dog, that constriction of a renal artery leads to marked reduction in the volume and sodium concentration of urine obtained from the involved kidney as compared with urine collected simultaneously from the opposite normal kidney. In applying White's observations for the detection of renal arterial

insufficiency in man [3,4], the test was first performed on a hypertensive patient with stenosis of the right renal artery (proved by aortography). As in the dog, the volume and sodium concentration of urine collected from the involved kidney was much less than that obtained from the opposite normal kidney at the same time. Recently Connor et al. [11] have reported the subsequent experience with this test at the Johns Hopkins Hospital, describing four patients in whom this procedure suggested a unilateral renal artery constriction. In two of them a stenotic lesion of the renal artery was demonstrated by aortography prior to operation. In the other two, aortography was not performed but there was evidence of ischaemic tubular

atrophy in the removed kidneys.

Since 1954 we have carried out sodium excretion studies on a total of 125 hypertensive patients at the Toronto General Hospital. There have been no false-positive tests. In every case in which there has been a significant reduction in the volume and sodium concentration of urine from one kidney there has been confirmatory evidence of renal ischaemia. * The results of these studies in the twenty patients operated upon are summarized in Table iv. In every case there was marked inequality of function of the two kidneys. In eight cases, the affected kidney excreted no urine, or so little that electrolyte determinations could not be made. In nine other cases the results were indicative of renal ischaemia, i.e., there was at least a 50 per cent reduction in volume and at least a 15 per cent reduction in the sodium concentration of urine collected from one kidney as compared with urine collected simultaneously from the opposite kidney. Subsequently evidence of renal ischaemia was obtained in all nine cases. Abnormalities of the renal artery were demonstrated in seven patients by aortography (unilateral renal artery disease, four patients; bilateral renal artery stenosis, three patients). In the remaining two cases in which differential function studies indicated renal vascular insufficiency, aortography was not performed but in both instances there was histologic evidence of renal ischaemia in the operative specimen: multiple atheromatous emboli with areas of ischaemic tubular atrophy in one (Case 6, Table v), and areas of ischaemic tubular atrophy associated with pyelonephritis in the other (Case 14, Table v). In the remaining

^{*} However, renal ischaemia need not be accompanied by hypertension.

TABLE V

indings Results	mall (90 1955-1958: Rescrpine ic pyelo- 1.0 mg. daily; head- aches and visual blur- ring cleared; blood pressure 180/100- 230/120 mm. Hg; October 1958, blood pressure 160/90; ocu- lar fundi normal	rosclerotic Greatly improved; left main blood pressure fell to normal postopera- gm.; is- rophy 75–195/85 mm. Hg; asymptomatic; no therapy; February 1958, ECG normal	y small Excellent; blood pres- lated by sure persistently nor- us tissue mal since operation in thick- ic pyelo-	areas of Greaty improved; lood pressure fell to normal after operation; January 1959, no headaches; blood pressure 140/80 mm. Hg. still a psychiatric problem	y 45 gm.; No improvement fol- clonephri- lowing nephrectomy; April 1958, blood pressure 230/150 mm. Hg
Pathologic Findings	Left kidney small (90 gm.); chronic pyelo-nephritis	Large atherosclerotic plaque in left main renal artery; left kid- ney 110 gm.; is- chaemic atrophy	Right kidney small and encapsulated by dense fibrous tissue up to 3 mm. in thick- ness; chronic pyelo- nephritis	Scattered slight isch ular atrop	Right kidney 45 gm.; chronic pyclonephritis
Aortogram	Not done	Not done	Not done	Stenosis right re- nal artery	Not done
Differential Renal Function Studies	February 1955: Right kidney, volume 33 ml.; sodium 2.1 mEq./L.; left kidney, volume 9 ml., sodium 15.7 mEq./L.	No urine flow from left kidney Not done	No urine from right kidney	Right kidney, volume 7 ml.; sodium 61 mEq./L.; left kid- ney volume 23 ml.; sodium 121 mEq./L.	Right kidney, volume 3.5 ml.; sodium 80.4 mEq./L.; left kidney, volume 22 ml.; sodium 80.9 mEq./L.
Pyclogram	Intravenous: no definite abnormalities noted; refragade: distortion of pelvis and major calyces of left kidney	Intravenous: non-func- tioning left kidney; retrograde: normal	Intravenous: small right kidney with dilated and deformed pelvis and calyces	Intravenous: normal ex- cept for slight dilatation of left renal pelvis which was not con- sidered significant	Intravenous: small poorly functioning right kidney
Clinical Features	dyspnoea; 1955. headaches; burred dyspnoea; 1955. headaches; blurred vision; refractory to hypotensive drugs; blood pressure 260/130 mm. Hg; grade un retinopathy; ECG, left ventricular hypertrophy; urine, specific gravity 1.030;* albumin negative; PSP, 15%, 15 min.; 42%, 1 hr.	1952: blood pressure normal; exertional dyspnoea for 1 yr.; digitalis and diuretics for cardiac failure for 3 mo.; blood pressure 210/120 mm. Hg; grade in retinogathy; ECG, left ventricular hypertrophy; urine, specific gravity 1.021;* albumin, trace; PSP, 12%, 15 min.; 45%, 2 hr.	Ten years previously right perinephric haematoma and urinoma developed following injury; since then occasional episodes of fever, loin pain and cloudy urine; hypertension first noted in 1953; blood pressure 185, 110 mm. Hg; no retinopathy; ECG normal; urine, specific gravity 1.026;* albumin 2+; PSP, 5%, 15 min.; 50%, 2 hr.	Hypertension during pregnancies in 1948, 1950 and 1953; recurrent anxiety and panic reactions since 1954; severe headaches; blood pressure 180/110-220/130 mm. Hg. fundi, arteriolar narrowing; ECG normal, urine, specific gravity 1,021;* albumin, trace; PSP, 25%, 15 min.; 75%, 2 hr.	Two-year history of hypertension; recurrent pulmonary ocdema for 1 yr.; blood pressure 190/130 mm. Hg; fundi, grade 1 changes; ECG, left ventricular hypertrophy; urine, specific gravity 1.016;* albumin 1.2+; PSP, 15%, 15 min.; 45%, 2 hr.
Diagnosis and Treatment	Unilateral pyelonephri- tis; left ne- phrectomy June 1955	Stenosis of left renal artery; left nephrec- tomy Febru- ary 1956	Perinephric fibrosis; right nephrectomy November 1956	Stenosis right renal artery; right nephrec- tomy Decem- ber 1956	Unitateral pyelonephritis; right nephrectomy December 1956
Patient, Sex, Age (yr.)	1, A. K., M, 52	2, W. P., M, 55	3, R. B., M, 22	4, M. I., F, 27	5, E. L., F, 47

Table v (Continued)

Results	Greatly improved; receiving no medication; asymptomatic; December 1958, fundinormal except for slight widening of light reflex; blood pressure 160/105 mm.	Greatly improved	Died of pulmonary oedema 48 hr. after operation	No significant change in blood pressure since nephrectomy	Severe postoperative shock resulting in death 48 hr. later
Pathologic Findings	Left kidney, multiple (atheronatous emboli occluding small intrarenal arteries; patchy areas of ischaemic tubular atrophy	Left kidney 110 gm.; generalized tubular atrophy compatible with renal ischaemia	Marked obliterative endarteritis of main, interlobular and arcuate arteries, with generalized atrophy and fibrosis of renal parenchyma	Multiple infarcts, right kidney	Similar to findings in Case M. T. (see text)
Aortogram	Not done	Not done	not visualized	Not done	Stricture of right renal artery pro- ducing marked narrowing of the lumen; similar lesion in left re- nal artery but only slight nar- rowing of lumen
Differential Renal Function Studies	Right kidney, volume 23 ml.; N sodium 121 mEq./L.; left kidney, volume 7 ml.; sodium 61 mEq./L.	No urine from left kidney	No urine from left kidney	May 24, 1957; (slow urine flow) right kidney, volume 1.5 ml.; sodium 56 mEq./L.; left kidney, volume 8 ml.; sodium 86 mEq./L.; May 26, 1957; (brisk diuresis) right kidney, volume 16 ml.; sodium 24.3 mEq./L.; left kidney, volume 102 ml.; sodium 19.4 mEq./L.	Right kidney, volume 5.6 ml.; sodium 20 mEq./L.; left kid- ney, volume 98 ml.; sodium 140 mEq./L.
Pyelogram	Intravenous: incomplete filling of middle and lower calyx of left kidney; otherwise normal; left retrograde normal	Intravenous: left kidney non-functioning and smaller than right	Intravenous: non-function of left kidney; hyper- trophy of right kidney	Intracenous: contracted small right kidney with a minor degree of cali- ectasis	Intravenous: right kidney smaller than left; other- wise normal
Clinical Features	Fatigue for 2 yr.; three-month history of severe headaches, exertional dyspnoea, weight loss; blood pressure 220/140 mm. Hg; fundi, grade in changes; ECG, left ventricular hypertrophy; urine, specific gravity 1.021;* albumin 2+; PSP, 20%, 15 min.; 45%, 2 hr.	Nine-month history of severe headaches, vomiting, dizziness; transient right hemiparesis; blood pressure 250/120 mm. Hg; grade II retinopathy; ECG; left ventricular hypertrophy; urine, specific gravity 1.018; albumin 4+; PSP, 20%, 15 min.; 75%, 2 hr.	from seminoma of testis in retroperitoneal lymph nodes 1952: onset of headaches and symptoms of heart failure; blood pressure up to 270/140 mm. Hg; recurrent pulmonary oedema since 1955; hypertensive encephalopathy for 6 mo.; unable to work despite intensive therapy with hypotensive drugs, digitalis and diurctics; grade II retinopathy; marked left wentricular hypertrophy; urine, specific gravity 1.014;* albumin 2+; PSP, 5 e., 15 min,; 50 e., 2 hr.	Chronic rheumatic heart disease, mitral stenosis and auricular fibrillation; 1955: mitral commissurotomy; blood pressure 180/115 mm. Hg; fundi normal; urine, specific gravity 1.023*, albumin 3-4+; PSP, 10%, 15 min.; 80%, 2 hr.	November 1955: hypertension discovered following miscarriage; headaches, fatigue and exertional dyspnoea for 1 yr.; blood pressure 260/160 mm. Hg; grade 11 retinopathy; marked left ventricular hypertrophy; urine, specific gravity 1.020; albumin 3+
Diagnosis and Treatment	Multiple ath- eromatous emboli in left kidney; left nephrectomy December 1956	Non-functioning left kid- ney; left ne- phrectomy December 1956	Postradiation atrophy and fibrosis of left kidney; left nephrectomy March 1957	Renal infarcts; right nephrec- tomy May 1957	Bilateral renal artery steno- sis; excision of stricture of right renal artery August 1957
Patient, Sex, Age (yr.)	6, T. H., M, 55	7, A. E., M, 55	8, J. N., M, 53	9, G. S., M, 47	10, I. A., F, 30

Table V (Continued)

Results	Blood pressure normal postoperatively ex- cept for occasional slight elevation; pa- tient died suddenly in March 1958	Blood pressure generally lower and occasionally normal post-operatively; 170/80 when discharged from hospital, but higher levels found later; died 4 mo. after operation of infectious hepatitis	sive (200/100 mm. Hg) but greatly improved; complete regression of cardiac symptoms; return of heart to normal size; considerable improvement in ECG; and subsidence of albuminuria, since nephrectomy; no medical therapy	Blood pressure normal since operation s s s c d s s s s s s s s s s s s s s s
Pathologic Findings	Left kidney 90 gm.; ischaemic atrophy	Right kidney 80 gm.; ischaemic atrophy	Right kidney 50 gm.; acute and chronic pyelonephritis with patchy tubular atrophy	Left kidney; pyohy- dronephrosis; arte- riolar nephrosclerosis with cortical atrophy; the cortical changes were considered to be more characteristic of arteriolar disease than of pyelonephritis
Aortogram	Stenosis, left re- nal artery with poststenotic di- latation	Stenosis, right re- nal artery	Right renal artery not visualized	Not done
Differential Renal Function Studies	Right kidney, volume 111 ml.; sodium 23.9 mFq./L.; left kidney, volume 5.2 ml.; sodium 2.8 mFq./L.	Right kidney, volume 7,5 ml.; sodium 12.3 mEq./L.; left kid- ney, volume 83 ml.; sodium 37.3 mEq./L.	No urine obtained from right kidney	Right kidney, volume 128 ml.; sodium 139 mEq./L.; left kid- ney, volume 5.2 ml.; sodium 88.6 mEq./L.
Pyelogram	Intrarenous: normal	Intrarenous: left kidney larger than right; slight clubbing and dilatation of calyceal system in upper pole of left kidney suggestive of chronic pyclonephritis	Intraemous: prompt ex- cretion of dye by both kidneys; left kidney nor- mal except for small calculus in minor calyx; right kidney contracted	Intravenous: enlarged functionless left kidney with staghorn calculus
Clinical Features	September 1953: blood pressure 128/70 mm. Hg; intermitent claudication, 3 yr.; progressive exertional dyspnoea. 1 yr.; angina pectoris, 2 mo.; headaches, 1 mo.; blood pressure 250/140 mm. Hg; grade II retinopathy; diminished arterial pulses in left leg; ECG; left ventrical pulses pertrophy; urine, specific gravity 1.017; albumin negative	Hypertension discovered 2 yr. previously; headaches, heart failure, visual difficulty and vertigo for 6 mo.; blood pressure 260/130 mm. Hg; grade 11 retinopathy; ECG, left ventrioular hypertrophy; urine, specific gravity 1.017;* albumin negative; PSP, 20%, 15 min.; 60%, 2 hr.	Known hypertension, 10 yr. up to 300 systolic; exertional dyspnoea, 5 yr.; blood pressure 270/140 mm. Hg; grade 11 retinopathy; ECG, marked left ventrihypertrophy; urine, specific gravity 1.021;* albumin 3+; PSP, 20%; 15 min.; 75%, 2 hr.	hypertension noted during routine examination; January 1958: pyuria noted on routine examination; frequent headaches; blood pressure 200/110 mm. Hg. slight narrowing of retinal arterioles; ECG, normal; urine, specific gravity 1,025; albumin 2+; many pus cells.
Diagnosis and Treatment	Stenosis, left renal artery; left nephrec- tomy January 1958	Stenosis, right renal artery; right nephrec- tomy Febru- ary 1958	Pyelonephritis; occlusion (?) of right renal artery; right nephrectomy March 1958	Staghorn calcu- lus with hy- dronephrosis and pyelone- phritis of right kidney; right nephrectomy April 1958
Patient, Sex, Age (yr.)	11, L. P., M, 47	12, A. O'H., F, 62	13, M. L., F, 45	14, E. P., F, 58

Table v (Continued)

)	ŀ	Renal Hyper	tension—I enat et e	21.	
Results	September 1958: blocd pressure 150/85 mm. Hg	Blood pressure persistently below 150/95 mm. Hg following operation	Blood pressure fell to normal postopera- tively, July 1958: ECG normal; Febru- ary 1959: blood pres- sure 145/100 mm. Hg	March 1959; blood pressure 160/95 mm. Hg	March 1959; Patient well; blood pressure normal; eyeground normal
Pathologic Findings	Left kidney 100 gm.; "chronic obstructive inflammatory proc- ess."	Similar to findings in Case M. T. (see text "the nature of the arterial lesion)"	Right kidney hydro- nephrosis and chronic pyclonephritis with marked atrophy and fibrosis of the cortex	Right renal artery narrowed by atheromatous plaque	Large infarct, lower pole right kidney
Aortogram	Not done	Multiple constrictions and sacculations of both renal arteries (Fig. 6)	The right renal artery did not fill; normal left renal artery and hypertrophied left kidney	Stenosis of right renal artery	Aneurysm on main inferior branch of right renal artery; no small branches supplying lower pole of right kid- ney; small right kidney
Differential Renal Function Studies	Complete stenosis of lower end of left ureter	Properative: right kidney, volume 13.5 ml.; sodium 18.0 mEq./L.; left kidney, volume 49.0 ml.; sodium 112 mEq./L.; postoperative: right kidney, volume ?; sodium 85 mEq./L.; left kidney, volume ?; sodium 77 mEq./L.	Right ureter partially obstructed half inch above ureterovesical orifice	Insufficient urine from right kidney for electrolyte determinations	kidney, volume 6 ml.; sodium 35.6 mEq./L.; left kidney, volume 8 ml.; sodium 51.2 mEq./L.; 7 gm. sodium 51.2 diet. right kidney, volume 5.5 ml.; sodium 4.3 mEq./L.; left kidney, volume 5.5 kidney, volume 5.5 ml.; sodium 4.3 mEq./L.; left kidney, volume 27 ml.; sodium 4.3 mEq./L.; left kidney, volume 27 ml.; sodium 4.3 mEq./L.; left
Pyelogram	Intracenous: nonfunctioning left kidney; compensatory hypertrophy of right kidney	Intravenous: normal	Intravenous: nonfunction- ing right kidney; retro- grade: hydronephrosis of right kidney	Intracenous: normal	Intracensus: (November 1958) shrinkage and de- formity of lower pole of right kidney since Au- gust 1958
Clinical Features	August 1957: hysterectomy for carci- mal; January 1958 laparotomy for abdominal mass which proved to be a blood cyst; intravenous pyelogram and blood pressure normal prior to this operation; April 1958; intracere- bral haemorrhage and left hemipare- sis; blood pressure 220/110 mm. Hg; grade III retinopathy; ECG, normal; urine, specific gravity 1.020; albumin negative	headaches for two years; blood prespressure 200/140 mm. Hg; grade 111 retinopathy; systolic bruit over abdomen and in right costovertebral angle; urine, specific gravity 1.022; albumin negative; PSP, 15%, 15 min., 45%, 2 hr.	Recurrent episodes of frequency, dysuria, right lower quadrant and right loin pain, and occasionally fever since age 18; October 1956; blood pressure 130/90 mm. Hg; September 1957; blood pressure 150/100; January 1958; blood pressure 170/110; April 1958; blood pressure 225/160; June 1958; blood pressure 225/160; June 1958; blood pressure 190/140; fundi normal; ECG, left ventricular hypertrophy; urine: albumin, trace; occasional white blood cells.	1954: appendectomy; blood pressure normal; exertional dyspinoea and headaches for two years; blood pressure 180/10 mm. Hg; grade in retinopathy; ECG, left ventricular hypertrophy; urine, specific gravity 1.019; albumin 1+	August 1958: acute episode of pain in right loin; blood pressure and intravenous pyelogram normal; October 1958: malignant hypertension with severe headaches and failing vision; blood pressure 180/120 mm. Hg; grade Iv retinopathy; urine, specific gravity 1.014;* albumin negative; PSP, 5%, 15 min.; 35%, 2 hr.
Diagnosis and Treatment	Stenosis, left ureter; left ne- phrectomy May 1958	Bilateral renal artery stenosis; repair, right renal artery June 1958	Stenosis, right ureter; liydro- nephrosis and pyclonephritis, right kidney; right nephrec- tomy June 1958	Stenosis, right renal artery; repair of right renal artery November 1958	Infarct of right kidney; right nephrectomy December 1958
Patient, Sex, Age (yr.)	15, A. L., F, 35	16, J. W., F, 35	17, G. S., M, 30	18, D. I., M, 47	19, J. Y., M, 33

* Maximum specific gravity obtained after eighteen hours of fluid restriction.

three (Cases 1, 5 and 9, Table v) there was a reduction in the volume of urine obtained from the involved kidney but the sodium concentration was either equal to or greater than that from the normal kidney. Two of these patients were not improved by nephrectomy and in the third the effect of surgery is uncertain. These patients, two of whom had unilateral pyelonephritis, will be described in more detail under the section on treatment.

It is of considerable interest that in all three cases of bilateral renal artery stenosis (patient M. T. and Cases 10 and 16, Table v) there was significant inequality of the function of the two kidneys with regard to urine volume and sodium concentration. We had thought that, when the vascular lesions were bilateral, the blood supply to each kidney might be impaired to a similar degree, resulting in equal function of the two kidneys. This has not been so in our cases. In one of these patients (Case 16, Table v) the vascular lesions were strikingly symmetrical on the two sides (Fig. 6) yet there was a marked difference in the function of the two kidneys. In Poutasse's case of bilateral renal artery stenosis [7] there was also a discrepancy in the sodium concentration of the urine obtained from the two kidneys; the urine volumes are not recorded.

Aortography. We have been guided by the results of the differential sodium excretion studies in determining whether or not abdominal aortography should be performed. If there are no significant differences in the volume and sodium concentration of the urine obtained from the two kidneys, it has been our practice not to investigate the patient further by aortography. On the other hand, a significant reduction in the volume and sodium concentration of the urine coming from one kidney is considered to be evidence of some renal arterial abnormality. In such cases, or when there is complete nonfunction of one kidney, we now believe that it is important to elucidate the nature of the arterial defect for two reasons. (1) The procedure of measuring volume and sodium concentration of the urine obtained simultaneously from both kidneys provides only a comparison of the arterial blood supply to the two kidneys. It is obvious, therefore, that a reduction in the volume and sodium concentration of the urine from one kidney, although practically diagnostic of some ischaemia of that kidney, does not guarantee the integrity of the blood supply to the opposite kidney. As happened with our case (M. T.), the

artery to the kidney producing a greater volume of urine of higher sodium concentration might also be abnormal. Therefore, one cannot confidently proceed to remove a kidney when differential function studies suggest impairment of its arterial blood supply without first demonstrating that the artery to the opposite kidney is normal. (2) An advantage of renal angiography is the possibility, in young persons, of demonstrating unilateral renal artery lesions which can be repaired by the vascular surgeon, thereby alleviating hypertension without loss of a kidney.

It is theoretically possible that differential urine volume and sodium excretion studies may prove to be normal in an occasional patient in whom hypertension is due to renal vascular disease. As mentioned, this has not been so in our cases of bilateral renal artery stenosis. Renal infarction is another situation in which one might predict relatively equal function of the two kidneys, especially if the zone of infarcted kidney were not very large, and if the arterial supply to the non-infarcted portion of the kidney were normal. In only one of our twenty cases was hypertension due to an infarct in one kidney. In this patient (Case 19, Table v), who had an infarct distal to thrombosis in an aneurysm of a branch of the right renal artery, there was a significant reduction in volume and sodium concentration of urine from the affected kidney when the test was performed at a time when the patient's sodium chloride intake was normal. It is our expectation that the number of patients with renal hypertension and normal differential function tests will prove to be exceedingly small. Nevertheless, we have recommended aortography in the occasional patient when the clinical picture strongly suggested the possibility of renal hypertension despite normal differential function studies. To the present time none of the patients falling within this group at our hospital have had renal artery lesions which could be demonstrated by aortography.

However, in another hospital we have recently seen a patient with hypertension secondary to renal infarction in whom renal function studies performed on two occasions demonstrated no significant difference in the volume and sodium concentration of the urine excreted simultaneously by the two kidneys. Because of a history of abdominal pain, and because the hypertension was of recent onset, there was a strong clinical suspicion of renal infarction in this patient. Aortography revealed an aneurysm

of a branch of the right renal artery supplying the lower pole of the kidney and there was evidence of impaired blood supply to a portion of the kidney distal to the aneurysm. Nephrectomy was performed and the patient's blood pressure returned to normal. An infarct was found in the kidney. Because of our experience with this case we suggest that aortography should be performed when the clinical picture is suggestive of renal infarction even though differential renal function studies are normal.

It should be pointed out that the plan of investigation as outlined here is not followed by all those who are active in the field of renal hypertension. Poutasse [6] considers renal angiography as the most important means of recognizing renal artery disease. In his clinic angiography is performed routinely on patients falling into the following four groups: (1) any hypertensive patient who shows unexplained disparity in the size or function of the kidneys by intravenous urography; (2) young patients who do not seem to have essential hypertension and who do not present any other demonstrable cause of hypertension; (3) elderly hypertensive patients in whom accelerated or malignant hypertension develops suddenly; (4) patients of any age with long-standing essential hypertension in whom the disease abruptly becomes more severe.

During a two-year period thirty of 104 hypertensive patients investigated in Poutasse's clinic were found by aortography to have unilateral or bilateral obstructive lesions of the renal artery. In only half of these patients did intravenous urography or renal function tests show specific alterations in size or function of the kidneys. The implication is that aortography should be performed in all patients suspected of having renal hypertension, irrespective of results of renal function tests, lest some cases remain undiagnosed. However, Poutasse does not describe the nature of the renal function tests used or the manner in which they were performed. We think it unlikely that, had differential volume and sodium tests been carried out on all his patients, normal results would be obtained in half of them. It is our contention that renal angiography is potentially too hazardous to be used as a screening procedure on all patients in whom the diagnosis of renal hypertension is considered. Reports of serious complications following aortography are appearing in the literature with disturbing frequency [12–15]. In expert hands the procedure may be

relatively safe but if angiography becomes routine practice in the investigation of patients suspected of having renal hypertension there is grave danger that it will often be performed by the inexperienced. The use of differential urine volume and sodium excretion studies has so far enabled us to keep the number of aortographic studies to a minimum and to predict accurately the presence or absence of an occlusive lesion of the renal artery.

Brust and Ferris [8] also believe that aortography has been of value in demonstrating lesions which would have been missed by other means of investigation. They report that differential renal function studies proved disappointing and were entirely normal in one of their patients subsequently cured by nephrectomy. Again, however, details are lacking as to the type of differential renal function tests employed and the manner in which they were performed.

We follow the procedure outlined by Connor and his associates [11] in carrying out renal differential function studies and interpreting results. Several points, however, are worthy of emphasis. The proper preparation of the patient is of utmost importance. The purposes of this preparation are threefold: (1) to provide adequate hydration; (2) to ensure an adequate concentration of sodium in the urine; and (3) to provide adequate sedation.

We have found a urine flow rate of 1 cc. per minute from each kidney to be ideal. If the rate of urine flow is much slower than this the time required for collection of adequate specimens is greatly prolonged and such tests are usually complicated by excessive bleeding into the urine. It is our practice to start an intravenous infusion of 5 per cent glucose in distilled water two hours before the test, and to run this at the rate of 500 ml. per hour. During the procedure the rate of fluid administration is increased if necessary to provide an adequate rate of urine flow. Oral hydration prior to the test has been less satisfactory in our experience since in many patients prepared in this manner nausea and vomiting develop during the procedure and this usually results in slow rates of urine flow. However, if the patient's history or examination is suggestive of cardiac decompensation, oral rather than intravenous hydration is desirable. The intake of sodium chloride must be sufficient to ensure an adequate concentration of sodium in the urine under conditions of moderate

AMERICAN JOURNAL OF MEDICINE

diuresis, i.e., at least 25 mEq./L. It has been our practice to give the patient a normal diet plus 6 to 8 gm. of extra salt daily for two days prior to the test. The salt loading is omitted, however, in patients with doubtful cardiac status. In our experience, sodium excretion studies may prove to be misleading when urinary sodium concentrations are low. In our case of renal infarction secondary to thrombosis of renal artery aneurysm (Case 19, Table v) differential renal function studies were carried out on two separate occasions: the first when the patient received 1 gm. of sodium chloride daily in the diet, and the second when the sodium chloride intake was 8 gm. daily. On both occasions the volume of urine from the infarcted kidney was much less than that from the normal kidney. Although there was a significant difference in sodium concentrations of urine from the infarcted and normal kidneys when the patient was receiving a normal intake of sodium chloride, this was not the case when the test was performed during the period of sodium chloride restriction

We have found that differential renal function studies performed under general anaesthesia have been unsatisfactory because of slow rates of urine flow obtained under these conditions. Cystoscopy and ureteral catheterization are performed under local anaesthesia whenever possible. Administration of sodium phenobarbital, 128 mg., and Demerol,® 100 mg., one hour and one-half hour, respectively, before the test has provided satisfactory sedation.

The cooperation of a urologist who is familiar with the basis of the test and its interpretation is essential. Ureteral catheters which fit snugly in the ureters (usually size No. 6), so as to prevent leakage around them, must be inserted to the level of both renal pelves. Trauma to the ureteral and pelvic mucosa may cause sufficient bleeding to interfere with the test. Slight blood staining of the urine, however, does not introduce enough additional sodium to interfere with interpretation of the test. The position of the catheters preferably should be checked by radiography. An observer must be present constantly while the specimens are being collected. Catheters not infrequently become partially or completely plugged by small blood clots. If the urine ceases to drip satisfactorily from one or both catheters the first collection period should be promptly terminated. The catheters may be cleared by syringing with small amounts of air,

after which another collection period is begun. One must ensure that the bladder is empty at the beginning of the collection period, and an indwelling catheter or cystoscope is allowed to remain in the bladder during the procedure. The accumulation of much bladder urine, signifying leakage around the ureteral catheters, invalidates the test.

It has been the practice of some to catheterize only one ureter and to assume that the bladder urine has come from the other kidney. This is unsatisfactory, since leakage around the one ureteral catheter may contribute to the bladder urine. Furthermore, it has recently been shown [16] that there may be a significant transfer of sodium across the bladder wall under the conditions which prevail during this procedure. Another variation of the technic has been to insert into the lower end of one ureter a catheter large enough to fit tightly and prevent leakage around it, and to collect urine from this catheter and from the bladder simultaneously. Again it is assumed that the bladder urine comes from the other kidney. In this instance one could safely assume that volumes were correct but, again, transfer of sodium across the bladder wall might lead to erroneous interpretations. Consequently we stress the importance of placing the ends of both catheters carefully within the renal pelves.

TREATMENT OF RENAL HYPERTENSION

Indications for Nephrectomy. A problem which not infrequently confronts the clinician is to know when to recommend nephrectomy in cases of hypertension associated with unilateral renal lesions. If it can be demonstrated by aortography, or by differential renal function studies, that the lesion is some abnormality which produces renal ischaemia, the chances of some worthwhile lowering of the blood pressure following surgery are reasonably good. On the other hand, when the unilateral renal disease is a disorder such as pyelonephritis, hydronephrosis or tuberculosis, surgery probably will not benefit the patient. In a disease such as hypertension, which may be associated with progressive renal damage, one is reluctant to reduce further the amount of functioning renal tissue by nephrectomy if there is a strong possibility that the blood pressure will not be lowered thereby.

Howard [17] has pointed out that differential renal function studies might be of value not only

in the detection of cases of renal hypertension but also in predicting which patients with obvious unilateral renal lesions will benefit from nephrectomy. All his patients who had a reduction in the volume and sodium concentration of the urine from the involved kidney were improved by nephrectomy. On the other hand, when nephrectomy was performed in four hypertensive patients with unilateral renal disease in whom the sodium concentration of the urine from the involved kidney was equal to or greater than that of the urine from the normal kidney, no sustained lowering of the blood pressure resulted. The volume of urine from the involved kidney in these four cases was significantly less than that from the normal kidney.

Our general experience in this regard has been similar to that of Howard. We have had six cases (Cases 4, 6, 11, 12, 14 and 19, Table v) of unilateral renal disease in which urine from the involved kidney was reduced both in volume and in sodium concentration. In every case nephrectomy was followed by a prompt fall in blood pressure, and this fall was sustained in all but one case (Case 12), in which a return of hypertension was reported prior to death from infectious hepatitis four months after the operation.

In our series of twenty cases there were three patients with unilateral renal disease falling into the group in which the volume of urine from the involved kidney was reduced but the sodium concentration of the urine was equal to or greater than that from the normal kidney. Two of these patients (Cases 1 and 5, Table v) had "unilateral" pyelonephritis with renal abnormalities readily detectable by pyelography. In one (Case 5) there has been no improvement following nephrectomy.* The other patient (Case 1) was deteriorating rapidly prior to nephrectomy despite therapy with hypotensive drugs. Following the operation there was no striking change in the blood pressure but during the next three years there was slow but steady improvement; at the present time the hypertension is no longer a therapeutic problem. It is difficult to assess the role played by nephrectomy in this patient's improvement. The third patient in this group (Case 9, Table v) was a forty-nine year old man with mitral stenosis and auricular fibrillation in whom hypertension

developed following mitral commissurotomy. There was also a history suggestive of peripheral arterial emboli. An intravenous pyelogram showed a small, poorly functioning kidney on the right side. The results of the differential urine volume and sodium excretion varied with different rates of urine flow. The volume of urine coming from the right kidney was always much less (roughly one-fifth) than that from the left kidney. During a period of slow urine flow the sodium concentration of the urine from the right kidney also was less than that from the left kidney. During periods of brisk diuresis, however, the sodium concentration of the urine from the small kidney was slightly greater than that from the opposite kidney. Aortography was not performed. The right kidney was removed and found to contain multiple small infarcts. The operation was unsuccessful in alleviating the patient's hypertension. It is likely that infarcts were also present in the left kidney.

Because of our general experience we are reluctant to advise nephrectomy when the so-dium concentration of the urine excreted by the diseased kidney is equal to or greater than that of the urine excreted simultaneously by the apparently healthy kidney. However, because of our experience with Case 1 (Table v), in which nephrectomy marked the turning point in the patient's clinical course, we believe that further observations will be necessary before one can consider failure to find a reduced sodium concentration of the urine from a diseased kidney to be a definite contraindication to nephrectomy.

The Role of Renal Artery Surgery. When hypertension is associated with unilateral lesions of the main renal artery, the choice of treatment lies between nephrectomy and surgical repair of the arterial lesion. In the older patient or in the poor risk patient, especially if there is evidence of arterial disease elsewhere, we believe that nephrectomy is the procedure of choice since arterial repair may involve a long and difficult operation. However, in the younger patient surgical correction of the arterial defect in order to preserve the kidney must be considered. This may possibly be the treatment of choice when the involved kidney is not completely functionless, as judged by urine excretion. In such cases, our own experience and that of Poutasse [7] would seem to indicate that restoration of the arterial blood supply will result in lowering of the blood pressure and improvement

AMERICAN JOURNAL OF MEDICINE

^{*} We have recently had a similar case, not included in this series, in which the blood pressure did not fall after nephrectomy.

in renal function. However, when little or no urine is excreted by the involved kidney it is probable that the renal ischaemia has been more severe or more prolonged and that irreversible atrophy of nephrons may have occurred. In such cases it is by no means certain that correction of an arterial defect would lead to restoration of a useful degree of renal function or to lowering of the blood pressure. Further experience and study will be required before the indications for renal artery surgery in the treatment of hypertension are clearly established.

When hypertension is associated with stenotic lesions of both renal arteries, restoration of the arterial blood supply by blood vessel surgery is the only feasible method of surgical therapy. The decision as to which artery to repair first may be a matter of considerable practical importance. We suggest that the artery supplying the more ischaemic kidney, as judged by sodium excretion studies, should be operated on first; in one of our cases it was necessary to repair only the one artery to produce satisfactory lowering of the blood pressure. The following case report (Case 16, Table v) illustrates this point:

J. W., a thirty-five year old woman, had hypertension in the range of 200/140 mm. Hg. Examination of her eyegrounds showed arteriolar narrowing and a few retinal haemorrhages. A systolic bruit could be heard over the abdomen. The intravenous pyelogram was normal but the volume and sodium concentration of urine from the right kidney was much less than that from the left. Aortography demonstrated multiple constrictions and sacculations of both renal arteries; these peculiar abnormalities were surprisingly symmetrical on the two sides. (Fig. 6.) However the results of differential function studies suggested that the ischaemic process was more severe on the right side than on the left; it was decided to repair the right renal artery first. In June 1958, the stenosed portion of the right renal artery was resected and the remaining portions of the vessel were then sutured together. No fall in blood pressure was predicted after this operation because of the lesion still present in the other renal artery. Much to our surprise, the blood pressure fell almost to normal and has remained in the range of 150/95 mm. Hg since then. This suggests that the lesions in the left renal artery are not interfering greatly with the blood supply to the left kidney. This suggestion was supported by postoperative differential function studies in which it was found that the sodium concentrations of urine obtained simultaneously from the two kidneys were now almost equal: 85 mEq./L. on the right side and 77 mEq./L. on the left. Unfortunately, leakage around the ureteral catheters made it impossible to compare urine vol-



Fig. 6. Patient J. W. (Case 16, Table v.) Aortogram demonstrating multiple constrictions and sacculations of both renal arteries. A marked fall in blood pressure followed repair of *only* the right renal artery.

umes on this occasion. No attempt will be made to repair the left renal artery while the patient's blood pressure remains in this relatively normal range.

Results of Surgical Therapy. Four of twenty patients have died. Two deaths were directly attributable to the operative procedures. In one patient (Case 10, Table v), who had bilateral renal artery stenosis, a precipitous drop in blood pressure developed following excision of a stricture of the right renal artery; the patient died of shock. The other patient (Case 8, Table v) had been having repeated attacks of pulmonary oedema prior to the operation and died of another attack during the immediate postoperative period. Two patients died within four months of operation: one of infectious hepatitis (Case 12, Table v), the other (Case 11) probably of myocardial infarction.

Sixteen of twenty patients are still alive. Although the period of follow-up in some of these cases has been short, at the present time we consider that twelve have been greatly improved by surgical measures. Complete cure cannot be claimed in all these patients since some have been found to be mildly hypertensive on one or more occasions since operation. Nonetheless, in these cases a severe, rapidly progressive disease, resistant to medical therapy, has been converted by surgery to a mild, benign and asymptomatic form of hypertension. We have observed this course of events in six of our twenty patients (Cases 2, 4, 6, 13, 17 and 18). The following two cases are typical examples:

W. P., a fifty-five year old man (Case 2, Table v), was found in the Medical Outpatient Department in

1955 to have a blood pressure of 210/120 mm. Hg. His blood pressure was known to have been normal three years previously but since then gradually increasing levels had been recorded. In the preceding year left heart failure had developed necessitating therapy with digitalis and diuretics, and he could not work. An intravenous pyelogram showed a nonfunctioning left kidney. During ureteral catheterization the left kidney excreted no urine. A left nephrectomy was performed in February 1956. There was a large atheromatous plaque in the renal artery and, on histologic examination of the kidney, patchy areas of tubular atrophy due to renal ischaemia were found. There was a prompt fall in blood pressure after the operation. At times normal levels have been obtained but on other occasions readings as high as 170/90 have been recorded. However, his heart failure has cleared, he is completely asymptomatic, requires no medication, and is doing full time work. Prior to operation his electrocardiographic tracings were indicative of left ventricular hypertrophy but they are now normal.

T. H., a fifty-five year old man (Case 6, Table v), was admitted to the hospital because of hypertension in December 1956. During the preceding several months he had experienced decreasing exercise tolerance, severe headaches, failing vision, undue fatigue, and was unable to work. His blood pressure was 210/130 mm. Hg. Examination of the ocular fundi showed marked arteriolar narrowing, retinal haemorrhages and exudates, and a suggestion of early papilloedema. The electrocardiographic tracing was that of left ventricular hypertrophy. An intravenous pyelogram showed only incomplete filling of the middle and lower calyces of the left kidney. Differential sodium excretion studies suggested ischaemia of the left kidney. Aortography was not performed. The left kidney was removed in December 1956. Histologic examination of the kidney demonstrated that many of the intrarenal arteries were occluded by atheromatous emboli; there were scattered areas of tubular atrophy due to renal ischaemia. Postoperatively the blood pressure fell to normal but, in the three-year follow-up period since then, has averaged 160/105 mm. Hg. The patient is completely asymptomatic, requires no medication and is doing full time work. At present the only abnormality on ophthalmoscopic examination is slight narrowing of the retinal arterioles.

In the remaining four of the sixteen living patients the results of surgical therapy may be classified as poor or doubtful. The blood pressure of patient M. T. (whose case was reported in detail at the beginning of this paper) fell to normal after both renal arteries were repaired but hypertension has recurred and there is again evidence of stenosis of the right renal artery. In

two patients (Cases 5 and 9, Table v) there has been no improvement following nephrectomy. In the fourth patient (Case 1, Table v) there has been slow but gradual improvement over a three-year period following nephrectomy, during which time the patient has also been treated with hypertensive agents. A rapidly downhill course prior to nephrectomy seems to have been reversed but it is difficult to be certain of the role played by the surgical procedure. It should be emphasized that Cases 1, 5 and 9 are the only three cases in the series in which there was not a consistent reduction in sodium concentration of urine from the diseased kidney when the test was performed under proper conditions.

SUMMARY

The diagnosis and treatment of renal hypertension are discussed in the light of experience gained at the Toronto General Hospital from 1954 to 1958. During this period we have studied twenty patients who have had either nephrectomy or renal artery repair in the hope of alleviating hypertension.

Differential sodium excretion studies have proved to be a useful and safe screening procedure for the detection of cases of renal hypertension, although false negative tests may rarely

occur.

Our experience also supports the observation that this test may aid in predicting which patients with obvious unilateral renal lesions will benefit from nephrectomy. In general, we have found that when the sodium concentration of the urine excreted by the diseased kidney is reduced the blood pressure falls after nephrectomy, but when this is not the case no improvement results. One possible exception to this statement has been encountered.

In cases of bilateral renal artery stenosis also, differential renal function studies are useful in determining which kidney is the more ischaemic. In one of our patients repair of the vessel supplying only the more ischaemic kidney resulted in a satisfactory lowering of the blood pressure.

The patients studied include three young women with bilateral renal artery stenosis. The underlying pathologic process common to all three of these patients appears to have been degeneration of elastica, and possibly muscle, in the media, followed by rupture and haemorrhage into the wall in the manner of a dissecting aneurysm, and subsequent organization of the haematoma.

The case report of one patient with bilateral renal artery stenosis is presented in detail. In this patient both arteries were repaired surgically and, following the second procedure, her blood pressure returned to normal and remained so for some months. However, hypertension subsequently recurred and there is evidence that the right renal artery is again stenosed.

Acknowledgment: We are grateful to our many medical and surgical colleagues who have permitted us to study their cases. We are also indebted to Dr. J. C. Laidlaw in whose laboratory the sodium estimations were performed, and to Dr. T. F. Nicholson, Department of Pathological Chemistry, who assisted in some of the renal clearance studies. We would also like to acknowledge the kind and helpful collaboration of Miss M. T. Wishart, Director of the Department of Art as Applied to Medicine.

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Effect of Thoracolumbar Sympathectomy on the Clinical Course of Primary (Essential) Hypertension*

A Ten-Year Study of 100 Sympathectomized Patients Compared with Individually Matched, Symptomatically Treated Control Subjects

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The over-all effectiveness of sympathectomy in the treatment of hypertension is still a highly controversial subject in spite of the extensive literature which has accumulated during the past twenty years [1]. This controversy persists even though it has been demonstrated repeatedly that the operation produces a significant, lasting reduction of blood pressure in a substantial minority of patients [2,3], and that it sometimes results in dramatic improvement in certain manifestations of the disease, especially retinopathy and papilledema. The effect of the operation on other important aspects of the disease is much less clear-cut and can be evaluated accurately only by comparison with the results of medical treatment in adequate control material. Most published reports [4,5] on the prognosis of medically treated hypertensive patients do not provide a satisfactory standard of comparison, because the clinical data on individual control subjects are not given in sufficient detail to permit the pairing of each surgically treated patient with a control subject suffering from hypertension of closely comparable severity.

Unfortunately, for a variety of reasons, a planned therapeutic trial in which patients

have been selected for medical or surgical treatment on a purely random basis has not yet been reported. There are, however, several studies in which the authors have tried, in retrospect, to subdivide the records of medically and surgically treated patients available to them into groups of approximately equal severity for comparative purposes [6-12]. By far the most extensive investigations of this type are those of Smithwick and his associates [6-8] who have graded the severity of the disease by means of a system which they devised especially for this purpose [2,7]. In the most recent paper of this series [8], the mortality rate of 1,608 surgically treated patients was found to be much lower than that of 619 patients who had been referred for consideration of sympathectomy, but in whom, for various reasons, the operation had not been performed. The data, which were presented separately for each sex and for each of the four severity groups, are summarized in

There are two important questions which may be raised regarding the validity of a comparison of this sort, namely, (1) does the use of the criteria on which the severity grading is based actually result in the subdivision of the clinical

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Table 1

COMPARISON OF FIVE-YEAR MORTALITY OF 619 MEDICALLY TREATED AND 1,608 SURGICALLY TREATED

HYPERTENSIVE PATIENTS*

			Ma	ales			Females								
Group		Surgica	1		Medica	1		Surgica	1	Medical					
	No.	Average Age (yr.)	Mortal- ity (%)	No.	Average Age (yr.)	Mortal- ity (%)	No.	Average Age (yr.)	Mortal- ity (%)	No.	Average Age (yr.)	Mortality (%)			
1 2 3 4	82 421 159 87	39 42 45 45	7 18 26 59	42 136 103 88	39 47 51 47	24 47 75 97	108 538 155 58	37 41 45 41	4 9 16 55	36 126 47 41	42 47 51 47	11 25 55 70			

^{*}Data compiled from Smithwick et al. J. A. M. A., 160: 1023, 1956.

material into groups whose members have a relatively uniform prognosis and (2) is there any evidence of systematic bias due to the presence in either the medical or the surgical series of an abnormally high proportion of patients whose prognosis is worse than the average of the severity group to which they belong? With respect to the first question, a few examples of the application of the Smithwick criteria [7] to hypothetical cases will serve to indicate that there is a distinct possibility that patients may be placed in the same group in spite of the fact that their clinical findings appear to differ widely in prognostic significance.* Consider, for example, two patients, one of whom is placed in group 4 because of the presence of marked nitrogen retention and a resting diastolic pressure of 130, while the other is placed in the same group because he is fifty years old and has an abnormal electrocardiogram, a resting diastolic pressure of 140 and an unsatisfactory blood pressure response to sedation. The short-term prognosis of the first patient is almost certainly poor, while that of the second might well be fairly good. A similar difference in prognosis might be assumed to exist between two patients in group 2, one of whom has retinal hemorrhages and has had a cerebrovascular accident with residual hemiplegia, while the other has normal fundi and no evidence of cardiovascular damage other than an abnormal electrocardiogram.

On the basis of Smithwick's published data,

the question of systematic bias within individual groups can be examined with respect to only one variable, namely, age. The figures in Table 1 show that, in seven of the eight sex and severity groups, the medically treated patients were, on the average, two to six years older than their surgically treated counterparts, the difference for the series as a whole being five years. Even though the effect of age on the prognosis of hypertension is quite complex, it is reasonable to assume that, all other things being equal, a five-year difference in average age would be reflected in the mortality rates at the end of a five-year period of observation. It is interesting to note that there was a similar discrepancy in the ages of the medical and surgical patients in the follow-up study of Hammarström and Bechgaard [9], the average ages of their 251 surgical patients and 435 medical patients having been 43 and 49.6 years, respectively. The modified Keith-Wagener-Barker system of grading used by these authors is even more likely to permit patients to be classified in the same group than the Smithwick system despite the presence of widely different degrees of organic damage. Unfortunately, the published data of Hammarström and Bechgaard are not sufficiently detailed to permit one to examine the possibility that the use of the Keith-Wagener-Barker system may have allowed a significant degree of systematic bias to occur with respect to variables other than age.

Smithwick [6,7] has frequently expressed his awareness of the limitations inherent in compari-

^{*} Smirk [14] has made similar criticisms of the Smithwick criteria in his recently published monograph.

sons based on the subdivision of clinical material into a small number of arbitrarily defined groups, and he has announced his intention, as soon as data become available on a large enough series of cases, to subdivide his surgically treated and medically treated patients into a larger number of groups "in each of which every important variable is the same." An attempt to achieve this ideal objective on a small scale has been made by Keith, Woolf and Gilchrist [10], who divided fifty-five surgically treated patients and seventy-four control subjects into a total of nineteen sex and severity groups matched as closely as possible with respect to age, Keith-Wagener-Barker retinal grade, cardiac and renal function, severity of symptoms, and diastolic blood pressure. They found that sympathectomy was more effective than medical treatment in producing symptomatic improvement, and that the operation reduced the mortality rate in patients with papilledema, but not in those with so-called "benign" hypertension. Unfortunately, the number of cases available to these authors was too small to permit adequate representation in all groups; therefore, their results must be regarded as inconclusive.

In one of the few controlled comparisons of medical and surgical treatment in which the cases were not subdivided into arbitrary groups, White, Dimond and Williams [11] and White [12] have studied fifty surgically treated hypertensive patients with definite cardiovascular complications and an equal number of medically treated control subjects with comparable complications, the two groups being closely matched with respect to age and sex. At the end of ten years the mortality in the surgical group (50 per cent) was strikingly lower than that in the medical group (96 per cent), but unfortunately no clinical data were given on the individual control subjects although a short case history was presented for each surgical patient.

The present investigation is an attempt to avoid some of the difficulties inherent in the use of a small number of arbitrary severity groups as the sole basis of comparison of medical and surgical treatment of hypertension. We have tried to broaden the criteria used in the selection of control subjects so that each patient treated surgically could be paired with an individual control subject of the same sex, and of similar age, blood pressure level, cardiac, cerebral, renal and retinal status. The principal shortcomings of the investigation are the relatively small number

of patients involved, and the fact that the criteria used to evaluate the "severity" of the disease are by no means free from the sources of error already discussed.

CLINICAL MATERIAL AND METHODS OF STUDY

Surgical Series. The surgical series consists of 100 patients in whom thoracolumbar sympathectomy was performed by Dr. R. H. Smithwick and his staff on the public ward services of the Massachusetts General Hospital between 1940 and 1945. The patients were the first fifty consecutive cases of each sex to be operated on by this technic, with the following exceptions: (1) as in a previous study which was limited to the effect of the operation on blood pressure [3], all patients who were not residents of the State of Massachusetts at the time of operation were excluded in the hope that this would make it easier to achieve a 100 per cent long term follow-up; (2) ten patients were excluded because there was substantial clinical evidence that their hypertension was secondary to some other condition (renal disease, seven cases; pheochromocytoma, two cases; coarctation of the aorta, one case);* (3) two patients were excluded because they died before the end of the tenth postoperative year as a result of conditions which were not considered to be direct sequelae of the operation or of the disease (postoperative pulmonary embolism in one case and perforation of a duodenal ulcer in another); (4) one patient who died of a cerebral hemorrhage before the second stage of the operation could be performed was excluded because a careful review of his record indicated that the first stage operation had probably not been a factor in precipitating the fatal complication; and (5) three patients who were otherwise eligible for inclusion were lost to follow-up; one refused to cooperate from the start, one was lost at the end of the first year, while the third was eventually located, but only after the make-up of the series had been decided upon and the pairing of the control subjects had been completed.

Most of the clinical and laboratory data on which the follow-up study of the surgical cases was based were obtained from the records of the Massachusetts General Hospital, especially those of the Hypertension Clinic, where most of the patients had been under the care of Dr. R. S. Palmer and his staff at various times, both before and after the operation. The files of patients who had never attended the Hypertension Clinic, and of those who became financially ineligible for clinic care during the follow-up period, were supplemented by data obtained by letter from their

^{*} Seven other patients in whom there was some evidence suggestive of pyelonephritis and three with a history of a recent episode of toxemia of pregnancy were retained in the series because these conditions were considered to be no more than incidental events occurring in patients with primary hypertension.

private physicians and from other hospitals to which they had been admitted for various reasons. In addition, almost all the surviving patients were subjected to special follow-up examinations in the Hypertension Laboratory of the Massachusetts General Hospital at times corresponding as closely as possible to the second, fifth and tenth anniversaries of the operation. The manner in which these examinations were carried out was described fully in a previous report on the project [3]. Most of the patients who moved outside the State of Massachusetts during the ten-year period were able to return to Boston for the follow-up examinations, but in three instances it was necessary to make arrangements for an internist in the patient's home town to perform the necessary investigations at our expense.

Control Subjects. The control subjects were selected from the records of three clinics which have been in operation for fifteen years or more, and which were organized for the specific purpose of collecting data on the course and prognosis of hypertension. The Hypertension Clinics whose records were available to us were those of the Massachusetts General Hospital, Boston, * the Columbia-Presbyterian Medical Center, New York, and the Royal Victoria Hospital, Montreal. Initially, the Montreal subjects were held in reserve, and a review was made of those in Boston and New York who had been seen prior to 1945 and who had been followed up for at least ten years or until death. As in the surgical series, all cases in which a diagnosis of secondary hypertension was established or strongly suspected were eliminated. With a few exceptions which will be noted subsequently, patients were also excluded if they had been treated with antihypertensive drugs (ganglionic blocking agents, hydralazine, rauwolfia derivatives, veratrum preparations or potassium thiocyanate).†

Numerical Code Used to Summarize Clinical Status of Patients. In order to facilitate the selection of suitable control subjects for the surgical cases, the "preoperative" clinical status of each patient in the surgical and control series was summarized by means of a simple, numerical code. In the surgical series the preoperative period was defined as the six months immediately preceding the date of operation, while in the control subjects the "operation" was arbitrarily assumed to have taken place six months after the patient's first visit to one of the cooperating institutions for the investigation or treatment of hypertension. The

*We are greatly indebted to Dr. R. S. Palmer for placing this group of cases at our disposal, and to Dr. Palmer and Dr. P. D. White for permitting us to supplement the Hypertension Clinic patients with a small number of their private patients whom they had kept under observation in a comparable manner.

† Patients were not excluded from the surgical series because they had been treated with antihypertensive drugs, either before or after the operation, but the fact that such treatment had taken place was indicated in the tabular presentation of the data. choice of six months as the baseline period was dictated by the fact that this interval was usually sufficient to permit the necessary clinical data to be collected, even in patients who were not admitted to the hospital.

The following is a summary of the criteria used in assigning grades to the fourteen parameters in terms of which the clinical status of each patient was described. The traditional semiquantitative 0 to 4 scale was used throughout, grade 0 being used to represent the normal and grade 4 to indicate an advanced degree of abnormality. The symbol "—" was used whenever the available data were too scanty or too inconsistent to permit a grade to be assigned with reasonable confidence.

Systolic blood pressure was graded on the basis of the average of all readings made in the lying or sitting positions under "casual" conditions, the grades being defined as follows: grade 0, under 140; grade 1, 140 to 169; grade 2, 170 to 199; grade 3, 200 to 229; grade 4, 230 and over.

Diastolic blood pressure was graded on a similar basis in terms of the following scale: grade 0, under 90; grade 1, 90 to 104; grade 2, 105 to 119; grade 3, 120 to 134; grade 4, 135 and over.

Orthostatic hypotension was evaluated in terms of the decrease in blood pressure which occurred on changing from the lying to the standing position. The decrease in pressure on standing was expressed as a percentage of the pressure in the lying position, separate calculations being made for systolic and diastolic pressure, and the average of the two values was graded as follows: grade 0, less than 5 per cent; grade 1, 5 to 14 per cent; grade 2, 15 to 29 per cent; grade 3, 30 to 44 per cent; grade 4, 45 per cent or more, or patient too faint to have pressure taken. Since the blood pressure of the control patients was not usually measured in the standing position, data on orthostatic hypotension are presented for the surgical series only.

Cardiac symptoms were graded as follows: grade 0, none; grade 1, slight dyspnea or retrosternal discomfort on moderate exertion, for example, climbing two or more flights of stairs rapidly; grade 2, definite dyspnea or anginal pain on exertion comparable to climbing one flight of stairs at normal pace; grade 3, dyspnea or angina while walking slowly on the level, or infrequent attacks of paroxysmal nocturnal dyspnea or acute coronary insufficiency; grade 4, left ventricular failure or congestive failure of sufficient degree to confine the patient to bed or chair, or angina decubitus or myocardial infarction.* (See footnote on p. 192.)

This system of grading differs from the New York Heart Association's classification of functional capacity in that it makes use of five grades, including grade 0, in order to conform to the pattern used in all other items in the present code. In addition, our system provides for automatic grading of certain specific complications, for example, myocardial infarction, regardless of the functional capacity of the patient

after recovery from the acute episode.

Heart size was assessed on the basis of the shape of the cardiac silhouette and the measurement of the cardiothoracic ratio on the 6-foot posteroanterior roentgenogram of the chest. The scale of grading was as follows: grade 0, cardiothoracic ratio less than 55 per cent, shape of cardiac silhouette judged to be within normal limits; grade 1, cardiothoracic ratio less than 55 per cent, prominent left ventricular contour on cardiac silhouette; grade 2, cardiothoracic ratio 55 to 59 per cent; grade 3, 60 to 64 per cent; grade 4, 65 per cent and over.

It is recognized that a system based on the tables of Ungerleider and Gubner [13] might have offered some advantages, but the necessary height and weight data were missing in too large a proportion of patients to permit the use of this standard of reference.

Abnormalities of the electrocardiogram were graded on the four-lead tracing only, because multiple precordial leads were not in routine use at the start of the follow-up period. The grading criteria were as follows: grade 0, T waves and ST segments, especially in leads I, II and IV, within normal limits; grade 1, T waves of low voltage (less than 10 per cent of the corresponding R waves), flat or slightly diphasic; grade 2, slight to moderate degrees of inversion of T waves or depression of ST segments; grade 3, fully developed ST-T pattern of left ventricular hypertrophy, or pattern characteristic of acute coronary insufficiency; grade 4, atrial fibrillation or pattern characteristic of old or recent myocardial infarction. Whenever the presence of ST-T changes due to digitalis therapy made it impossible to apply these criteria with certainty, the electrocardiographic grade was represented by the symbol "-".

Headache was included in the list of graded items, in spite of the notorious difficulty in quantitative evaluation of this symptom, largely because the ability to relieve headache has often been listed as one of the most consistent results of thoracolumbar sympathectomy. The criteria used were as follows: grade 0, headache within normal limits with respect to frequency and severity; grade 1, more frequent or severe than normal, but not usually requiring analgesics for relief; grade 2, requiring medication, but not severe enough to interfere with work; grade 3,

severe enough to interfere with ordinary activities; grade 4, incapacitating, requiring bedrest or opiates for relief. Classic migraine, regularly relieved by the administration of ergotamine, was graded "—".

Cerebrovascular accidents (CVA) were arbitrarily defined to include the whole gamut of sensory and motor manifestations of diffuse and focal hypertensive vascular disease of the brain. Grade 1 indicates the occurrence of one or more brief attacks of numbness or clumsiness of a portion of an extremity or of the face. Grade 2 indicates either (1) an unmistakable "stroke" with definite loss of motor or sensory function, followed by complete recovery within a few hours or days, or (2) the syndrome of acute hypertensive encephalopathy with headache and/or mental confusion, but without coma or convulsions. Grade 3 implies the occurrence of either (1) hemiplegia (or hemianesthesia or hemianopsia) with slow, but nearly complete, recovery of function, or (2) acute hypertensive encephalopathy with prolonged coma or convulsions or (3) subarachnoid hemorrhage without evidence of intracerebral extension. Grade 4 was reserved for strokes resulting in permanent loss of function of 50 per cent or more, including the syndrome of chronic hypertensive encephalopathy (multiple small strokes) with severe, progressive, mental deterioration.

Renal symptoms are probably the manifestation of hypertension which lends itself least readily to inclusion in any system of numerical grading. Nevertheless, in the interest of completeness, an attempt was made to record the presence of such symptoms in terms of the following scale: grade 0, absence of nocturia (the examiner is expected to make all possible effort to differentiate between true nocturnal polyuria and simple nocturnal frequency due to insomnia or excessive ingestion of fluids); grade 1, nocturia usually once and sometimes twice each night; grade 2, nocturia more than twice nightly; grade 3, symptoms suggestive of early uremia; grade 4, clinical uremia with marked symptoms such as coma and

convulsions

Proteinuria was graded on the ordinary 0 to 4 plus scale used in the clinical laboratory, our grade being based on the average result of all tests performed during the period in question. Tests in which the result was recorded as "trace" were arbitrarily grouped

under grade 1.

Renal function was graded on the basis of urinary concentrating power (SG), the ability to excrete intravenously injected phenolsulfonphthalein (PSP), and the concentration of non-protein nitrogen in the blood (NPN). Since almost all the common sources of error in the SG and PSP tests tend to give falsely low results, whenever there was a discrepancy between the grades assigned to the results of these two tests, the one indicating the better renal function was accepted as correct. The over-all renal function grade was based on the following criteria: Grade 0, maximum specific

^{*} This section of the code would probably have been of greater value if it had been subdivided into two separate sections; one for various degrees of myocardial insufficiency from slight dyspnea to congestive heart failure, and one for various degrees of coronary heart disease from slight angina to myocardial infarction. In this study it was believed that the data were not always sufficiently complete to permit this to be done, but the dual system of coding will be used in future applications of the system in the documentation of the natural history of hypertension.

gravity 1.025 or more, or one hour PSP excretion of 60 per cent or more; grade 1, SG 1.015 to 1.024, or PSP 45 to 59 per cent; grade 2, SG under 1.015, or PSP under 45 per cent, NPN normal; grade 3, NPN above the upper limit of normal, but under 60 mg. per 100 ml.; grade 4, NPN 60 mg. per 100 ml. or over.

Abnormalities of the retinal vessels were evaluated on the basis of a composite assessment of generalized and localized arteriolar narrowing, abnormalities of the light reflex and arteriovenous crossing phenomena. In almost all the surgical patients and in nearly half the control subjects, the fundi were examined and graded by the same ophthalmologist,* using a system in which "hypertensive" changes (mainly arteriolar narrowing) and "arteriosclerotic" changes (abnormalities of light reflex and arteriovenous crossing phenomena) were graded separately on a 0 to 4 scale. In such cases the average of these two grades has been recorded, fractional values having been rounded off in the direction of the "hypertensive" grade. In the remaining cases, the written reports of various ophthalmologists have merely been translated into our numerical scale, using grade 1 for slight or mild changes, grade 2 for moderate, grade 3 for marked, and grade 4 for very marked or extreme changes, including occlusion of the central retinal artery or its major branches.

Retinopathy was taken to include retinal hemorrhages and edema as well as "exudates" (cotton-wool patches and edema residues). The grades refer to the condition of the worse eye, using the following scale: grade 1, retinal edema, or occasional hemorrhages and/or "exudates" (not more than a total of four in both fundi); grade 2, numerous scattered hemorrhages and/or "exudates"; grade 3, extensive hypertensive retinopathy with beginning formation of a star figure at the macula; grade 4, fully developed picture of hypertensive retinopathy with bilateral macular stars.

Papilledema was also graded on the basis of the condition of the worse eye, the criteria used being as follows: grade 1, definite edema of the nerve head with pathologic blurring of the margin, but without measurable elevation; grade 2, elevation of about 1 diopter; grade 3, 2 to 3 diopters; grade 4, 4 or more diopters.

The criteria used to define the various grades in the code adopted have many obvious shortcomings, some of which have been referred to in the text. The only advantage of the system is a relative freedom from ambiguity which makes it possible for independent observers to assign almost identical grades when assessing the same record. For example, during one stage of the study a group of records which had previously been graded by one of us (K. A. E.) was regraded independently by another (H. T.) shortly

* We are greatly indebted to Dr. David Cogan, Director of the Howe Laboratory of Ophthalmology, Massachusetts Eye and Ear Infirmary, for performing the fundus examinations on these patients.

after he became associated with the project. Of a total of nearly 4,000 individual grades, a discrepancy of one grade was noted in only 5 per cent, and there were only eight instances in which a discrepancy of two grades occurred.* The accuracy of the grading is, of course, limited by the reliability and completeness of the original records and follow-up examinations, and, in the case of subjective symptoms such as headache and dyspnea, it is critically dependent on the patient's reliability as a witness. Despite these limitations, we believe that errors of two grades in the coding of any item are rare, largely because we have not hesitated to use the symbol "-" whenever the information was too scanty or too vaguely expressed to permit the grading criteria to be applied with reasonable confidence.

Selection of Matched Control Subjects. During the selection of the control subjects, those in charge of matching (M. M. S. and W. P. C.) had access only to the preoperative clinical profiles of the surgical propositi and the potential control subjects from the Boston and New York series. Each profile identified the corresponding patient in terms of serial number, sex and age, and listed the preoperative grades for each of the parameters described in the previous section. Starting with the coded data for any one surgical case, the authors in charge of matching tried to select from the control pool of patients of the same sex and of similar age, one or more control subjects whose grades resembled those of the propositus at least as closely as

required by the standards to be described.

Because of the established prognostic significance of papilledema, no exception was permitted to the rule that, if papilledema had been present in the propositus during the preoperative period, it must also have been present in the corresponding control subject. A similar absolute requirement would have been insisted on with respect to nitrogen retention, but this problem did not arise because there were no patients in the surgical series in whom nitrogen retention had been present before the operation, this finding having been accepted as an absolute contraindication to sympathectomy throughout the period covered by the study. Cerebrovascular accident was another preoperative finding with respect to which we were anxious to avoid discrepancies between propositus and control subject. Such a discrepancy was permitted in a few instances, but only if the cerebrovascular accident in question were of no more than grade 1 severity, and then only if this discrepancy were counterbalanced by a difference in the opposite direction in other items in the clinical profile. When searching for control subjects for patients in whom neither papilledema nor nitrogen

^{*} In this instance, and on all other occasions when different grades were assigned to the same item by two independent observers, the records were submitted to one of us (W. P. C.) for reassessment, and his grading was accepted as final.

TEN YEAR FOLLOW-UP DATA ON HYPERTENSIVE PATIENTS TREATED BY THORACOLUMBAR SYMPATHECTOMY AS COMPARED WITH MATCHED CONTROL SUBJECTS TREATED SYMPTOMATICALLY Male Series

	Death	Time	Post- opera- tively (mo.)				30	37	88 5	20	2 : 8	21.						: :	
	ď		Cause					CH	H.E.	IMI		CVA	* * * * * * * * * * * * * * * * * * *	* * *			* * *		
	, 2		pille- dema	0-08	0000	9 9 9 9	90	0000	18	10	311-	000	0-00	0-00	000	100	00-0	000	0000
Retina	Grade 0,2,5,10 Yr.	3	nop- athy	1 700	0000	0-00	90	1000	100	98	1100	9000	0000	0000	00-0	-0-0	000	-000	0000
	0,3		Ves- sels	11-2	1000	0-000	1000	2222	233	23.23	2222	11-2	01-1	000	9=	20-0-0-0-0-0-0-0-0-0-0-0-0-0-0-0-0-0-0-	0-12	000	-121
	1	05	PSP.	0-08	18	0000	90	0001	0-0	55	0-00	1011	11-0	0-00	2-22	-00	900	-000	0-10
Kidneys	Grade 0,2,5,10 Yr.	Den	tein- uria	98	0-10	0-00	90	0-00	000-	03	0-00	111-	0000	21-0	2001	000	00-0	1-0-1	
	0,2		Symp- toms	0000	0000	0000	0001	0000	-000	92	0000	1111-	0000	0000	0000		-	-0000	
u	le Yr.		CVA	0000	0000	0000	0000	2000	304	00	0000	3204	0000	0000		-000	0000		
Brain	Grade 0,2,5,10 Yr.	-	Head- ache	0000	0000	2211	0000	1001	20-	10	3111	2010	0000	0000	0000	-000	0000	-0000	2111
			DOG	000-2			23-2	1011	112	= 23	25 52	3333	22-3	2-22		-0-0-			1-11
Heart	Grade 0,2,5,10 Yr.		Size	1000		0000	1-1-0	11-11	1=	= 7	0-0-	221-	0012	0000	0000	0-0-			1-11
0.2.0	0,2,		Symp- toms	01112	1112	1000	000-3	00001	000-	23	0000	2133	10-3	0000	1111	-100	0000	100-	1-11
			Fall Fall	00:	00-0	9:	-00	1211	ē :	7:	0-10	-00 :	0:	9:	0000	þ :	001-	-120	-100
	Grade 0,2,5,10 Yr.	-	Diag- tolic	23-2	3-33	22-2	2-2-2	2222	344	34.	3-21-2	2010	222-1 2223	32-1 2322	3111	3-22	3222	3344	3223
	0,2,		tolic	13-3	1-22	22-1	22-2	2122	334	34	3-23	2011	2223	2212	2000	2-1-2	2222	2222	2222
(mm. Hg)	nly)	rative	Minimum	124/80	114/80	134/82	140/100	116/80	134/84	140/60	140/70	120/65	144/88	122/88	112/64	116/78	118/78	60	124/72
Blood Pressure (mm. Hg)	Range tting Pressures Only)	Postoperative	Maximum	230/140 215/140	200/148 220/140	182/132	210/148 220/134	218/132 240/145	220/118 280/165	180/110	195/130 220/120	170/124 220/130	182/118 235/145	162/120	163/125 222/148	170/120 190/138	180/138	136/110	264/136
B	Rang (Lying and Sitting	rative	Minimum	128/74 150/100*	104/70	146/100 152/96*	140/90	110/68	134/96	150/90 190/125	158/82 210/130*	140/80	156/110 160/100	150/90	130/90	118/52	134/78	140 90	150/96
	(Lying	Preoperative	Maximum	200/130 210/130	180/140 200/130	190/122 180/125	188/150 200/150	225/120 230/125	250/144 260/140	210/120 270/160	204/130 240/140	215/125 204/130	220/120 200/130	190/144 200/140	230/150	188/140	190/145	204/150 195/150	200/134
glia	pan	2nd	Stage	₩ :	9-2	8-1	8-1	10-2	6-2	. 8-1	8-1	- :	00 :	-8 :	9-5	1-6	8-2	9-5	1-6
Gang	Kemoved T-L		Stage	- · ·	9-2	7-1	- 8 :	6 :	8-3	8-5	8:	- co	8 :	œ :	7-1	5 :	9-2	8 :	9-5
	Known Dura- tion of			16	10	18 mo. 5	15	6 mo.	18 mo. 3	CM ~13	च च	7-1	91-	2 mo. 6 mo.	50	3.1	4 mo. 6 mo.	90 m	7 6 mo.
	Fam- ily His-	tory		1+	++	++	++	++	11	1+	11	11	++	++	+1	++	++	p-	11
	Age (yr.)		-	44.5	40.2	22.9	34.0	38.7	40.0	41.5	41.8	42.9	48.0	18.4	24.3	26.6	32.0	32.3	33.6
No. (Sase			15	25 20 20				85 85	22			-	11S 11C	12S 12C	13S† 13C	14S 14C	15S† 15C	16S 16C	

AMERICAN JOURNAL OF MEDICINE

	92		39	81	53	105 108	15	* * * * * * * * * * * * * * * * * * * *	54	86	57	: :	34		115	::	22	10		17 22	:::	32
	IM		CH	сн, п	СН	MM	CVA HF, MH	::	HF, U	Ú	HF		CH		HF, MI	: :	MH	СН	: :	HF		СН
0000	000-	0000	0000	0-0	1-00	10	100	0000	000	0000	-000	0-00	0-1-0	20-0	0000	0000	23.23	30	0000	00	0000	11
0000	000-034-	0000	0000	00	9-00	100	100	10-0	010	0000	-000	000	10	0-05	0000	0000	34	3353	0000	12	0000	2-1-4
2-00 0011	110-	$\frac{1-12}{112}$	2222	2-1	3-01	1 1	1_	$\frac{11-1}{2223}$	2223	1110	122-	2-00	27	0-04	1-1-0001	1000	777	65 65	2011	33	33-0	-5
000	000-	00-00	000	000	1-11	1-1-1	100	1000	034	0011	01111-	00-0	17	0-00	0000	0000	24.4	14	0000	000	000-0	1-1
0000	000-033-	0000	-001	0-13	00-00	100	-0	0-00	132	1000	-100	0000	11	0-00	0000	1-00	333	253	0-10	1-04	000-0	2-1-4
0000	111-0	0000	-000	100	0000	-000	-0	0000	224	2114	-100	0000	11	1000	0000	0000	14	63 63	10000	1=	0000	<u>-1</u>
0000	-000	2000	0000	3001	0000	100	13	0000	003	1100	000-	0000	77	0000	0000	0000	00 00	22.2	0000	-00	0000	24
1100	-000	0000	0000	100-	1001	-000	===	1100	122	2000	000-	0000	1-3	2000	0003	2000	32	40	0000	23	00000	10
1124	000-033-	2111	22-3	1 00	0000	2-2-2	01	20-0	333	0000	21-	0-04	2-4	0-00	1-24	000	22	24	1011	12	2011	2-2
0-00	2-2-	0-00	25-2	010	0-00	0-0-0	1-1	21-1	334	1111	11-	000	1-2	0-00	0-0-0	0000	2-	23	0000	010	1011	0-1-1
00000	0004	1000	3334	1111-	0000	000-4	14	1221	334	0011	004	212-	2-4	0000	00014	0000	13	50 50	1000	904	3000	0-1
0000	-020	0-10	2	8	0110	1 :		0-0:	-08	-120	-00	-121	1:	0-1	-50-	Ŧ:	-0 :	= :	000-	-0	-2-1	01
3001	323-	3223	25 25 25 25 25 25 25 25 25 25 25 25 25 2	3233	34	30	Is	3333	332	3334	332-	3110	5 7	12-1	1344	4-11	44	7.7	4222	44	41-2 3223	44
2001	222-	2123	2222	2233	2001	222-	33	323	332	3334	33-	3210	17	-100	3234	3-01	33	33	3111	3-	3322	34
84/58	116/62 150/80	80/40 122/80	120/100 165/110	95/62 160/100	104/72	118/80	84/46	160/100	128/68 150/110	88/60 210/120	130/90	110/70	150/90 200/120	124/80	150/110	115/80	160/80	134/70 200/125	120/80 144/98	130/70 240/140	120/78 150/110	120/100 190/140
148/112	280/172	226/132 250/140	200/158	236/140	166/110	202/130 220/130	260/165 265/162	242/144 230/160	250/160 275/110	170/120 290/145	244/152	206/120 252/155	240/160	180/120	240/180 215/155	168/112 250/150	240/156 250/160	240/160	163/125 240/148	213/150 280/164	185/125 245/160	260/162 260/165
130/90	180/80	135/80 160/102*	130/90	148/90	102/50	120/98	130/72	156/90	130/72	178/110*	150/95 200/116*	150/94 150/100*	180/100 230/140	150/100	178/128	148/90	170/110 220/120	186/102 190/110	180/108 140/80 *	140/90 180/110	182/110 160/100	186/118 210/130
200/145	220/148	194/140	215/150 220/140	225/130 230/155	220/160 210/140	236/150 236/150	220/162 250/152	252/164 230/156	220/140 260/170	224/154 235/140	240/150	260/140	245/150 260/160	226/180	230/170 240/160	225/160 265/160	256/162 265/175	242/160 250/150	238/170 240/140	245/170 260/160	240/170 240/150	250/150 270/180
1-6:	9-2	12-1	1-01	92	9-1	2-2	9-1	- : :	2-01	9-5	8-2	9-1	9-2	8-1	9-2	8-5	9-2	9-5	- : :	9-5	8-5	9-2
9-2	9-5	9-1	10-2	9-3	10-1	67 :	9-1	-8 :	10-1	9-2	2-8	7-2	9-5	-8 : :	9-1	9-5	9-5	9-5	8-1	9-1	8-1	9-5
0100	2 6 mo.	03.40	10 6 mo.	3 mo.	2 mo.	1	71	1-10	10	10.03	10.4	E- 60	10	2 mo.	8 mo.	3 6 mo.	10	3 mo.	12	3 mo.	123	2 mo.
+1	+,.	e - 1	1.1	•+	0.0.	‡+	1+	++	++	+1	11	10-	11	1 :	‡+	++	++	++	11	0.0.	++	+0.
32.8	35.9	36.4	38.4	40.7	42.8	43.6	39.8	31.3	40.5	42.1	45.6	48.1	53.4	18.2	26.4	37.0	38.0	41.8	42.0	43.2	44.3	47.3
17S 17C	18S 18C	19S 19C	20S 20C	21S 21C	22S	23S 23C	24S 24C	25S 25C	26S 26C	27S 27C	28S 28C	29S 29C	30S 30C	31S 31C	32S 32C	33S 33C	34S 34C	35S 35C	36S 36C	37S 37C	38S 38C	39S 39C

TEN YEAR FOLLOW-UP DATA ON HYPERTENSIVE PATIENTS TREATED BY THORACOLUMBAR SYMPATHECTOMY WITH MATCHED CONTROL SUBJECTS TREATED SYMPTOMATICALLY Table II (Continued)

Male Series

	,			,	-, -	0		001			-,	Per	cci	13101		Lil	vei)
	Death	Time	Post- opera- tively (mo.)	112	2.4	ŀ	-1-	99		29	14	. 4	80 cs	23 23	24	85	6 days
	ď		Cause	HE, U	H		HF, U	MI	100	HF, U	MH	MI	MH	n W	МН	нЕ, мн	PO, MI
			Pa- pille- dema	9	0000	0000	÷	1000	000	005	1	10-	22	11	22	100	-0
Retina	Grade 0,2,5,10 Yr.		Reti- nop- athy	00	2010	1000	53	0000	2-00	212	4	-00	3 2	, l	22	2-3-	-000
	0,3		Ves- sels	00	2222	3-	233	2122	1-12	- 2		323	£ 53 :	+ +	34	3-3-	323
	1	1 5	PSP.	7:	11 19	0111	24	11-1	2-23	534		100	24	5 1	-	0-14	133
Kidneys	Grade 0,2,5,10 Yr.	-	tein- uria	-1-0			23	21-1				222	-5:	‡ ±:		1-13	0-
	0,2		Symptons	0000			10	-110	E			000		1		022-	0-0
in	de 0 Yr.		CVA	0000	1000	0110	00	-000	0000	9-		000		3 98	~		-000
Brain	Grade 0,2,5,10 Yr.		Head- ache	302-	0000	0-	90	211-	0000			901	-61		-		2- 100
	1		ECG	-001	33-3	1-	53	22-	2334	1	::	114	1-	-1:	-		234
Heart	Grade 0,2,5,10 Yr.		Size	0 0	0 11	771	1	-10	12-2	0		000-	1=	: ==	-		55 55
	0,2		Symp- toms	0000	00002	-0	13	0-0	21-		:::	024	88		-		224
			tural Fall	-020	Ę	. 7	:	-10	10			000	-0	+	101-	:	1:
	Grade 0,2,5,10 Yr.	-	Dias- tolic	4234	4222		44	333-	3112	11	:	##	7.7	++	~~ .	-	1 2 2
	0,3		sys- tolic	3133	3122	33		3-	4012	+		11	44	+ +	4224		433
(mm. Hg)	nly)	rative	Minimum	122/86 156/90	140/80	140/86	011/211	200/100	90/60	172/82	:	170/110	130/72 205/140	150/90	122/78		011/061
Blood Pressure (mm. Hg)	Pressures Only)	Postoperative	Maximum	225/150 220/138	212/130	220/130	070 / 110	280/155	204/125 262/160	256/190		280/212 280/176	250/160	245/150	-		240/150
B	Range (Lying and Sitting P	ative	Minimum	158/92	192/104*	140/100		200/100*	160/98	180/100	*******	160/92 200/110*	160/80 205/140	190/120 200/140	190/118		170/100
	(Lying	Preoperative	Maximum	250/160 240/152	230/170 300/180	250 172 260/150		280/155	260/158 240/180	260/220	_	280/195 260/170	250/188 250/180	270/190	264/170		250/160
dia	2	2nd	Stage	10-2	9-3	7-2	6-3	:	œ :	9-1		9-5	10-2	8-3	8-5	6-8	:
Ganglia	T.		Stage	9-1	9-5	8-2	7-3	:		2-2		dz ;	9-5	% : ∞ :	6-3	2	:
	Known Dura- tion of			2 mo.	9 9	710	8 mo.	2	9 mo. 6 mo.	1 mo.		3 mo.	10	1 mo.	18 mo.	50	6 mo.
	Fam- ily His- tory			1+	++	e-+	1	+	1+	1		1 1	+1	+1	++	1	1
Age (yr.)				48.7	18.9	51.6	48.3	44.6	51.2	11.0	# 00	22.9	30.1	41.3	46.4	50.7	50.0
Case No.					41S 41C	42S 42C	438		44C	458 45C			478 47C	48S 48C	49S 49C		20C

Nore: S = surgically treated patient; C = control patient, that is, one who had received only symptomatic treatment, T = thoracic; L = lumbar; BP = blood pressure; ECG = electrocardiogram; SG = specific gravity of cerebral bemorphage; CVA = cerebrovascular accident; U = uremia; MH = "malignant" hypertension; PO = postoperative complication; +H = history of hypertension in both parents; += history of hypertension in one a parent of in patient's sibilings; ? = doubtfully positive family history of hypertension; PO = postoperative complication; +H = history of hypertension in one a pressure selected from available. "blood pressure readings because no pressures taken under resting conditions in hospital were available on these patients.

† The grades for all items in the ten-year follow-up data of these two patients have been shown as "-" because they declined to pressure grades for at ten years. However, since they were followed for at least five years and are known to have been alive and well at ten years, they have been retained in the series and it will be assumed that their blood pressure grades at ten years were the same as at five years. 29

retention nor cerebrovascular accident had occurred, similar compromises were permitted with respect to minor discrepancies in the cardiac, renal and retinal findings. Because of the relatively low prognostic significance of a difference of one grade in the individual items in these three sections or "panels" in the profile, it was considered satisfactory to match the grades of all the items in any one panel as a group. For example, it was permissible for a surgical patient to have a higher electrocardiographic grade than the corresponding control subject, provided there was a similar discrepancy in the opposite direction in heart size or cardiac symptoms. Headache was the only item in the profile which was ignored in making the selection of the control subjects.

In many instances application of these criteria narrowed the search for a suitable control down to a single case, but usually there were two or more possible control subjects with data which involved only minor discrepancies from those of the corresponding surgical patient. Whenever this occurred the preoperative data were submitted to the others, and the selection of the most satisfactory match was made on the basis of a majority decision. In fourteen instances it was decided that none of the control subjects suggested by those in charge of matching was entirely acceptable; therefore, it was necessary to turn to the Montreal cases for more suitable replacements. This phase of the project involved a departure from the technic of "blind" matching which had been used up to this point, because the one (K. A. E.) responsible for the grading and selection of the Montreal control subjects was personally familiar with the followup records of these patients and also had access to the postoperative records of the surgical patients. Despite this admitted shortcoming; every effort was made to avoid the introduction of bias in the selection of the twelve control subjects who were eventually supplied from the Montreal series, and examination of the protocols of these subjects and the corresponding propositi (No. 35, 40, 44, 57, 63, 70, 82, 84, 87, 93, 95 and 100 in Tables II and III) does not reveal any evidence of such bias in either direction.

Finally, however, when all our control material had been exhausted, there still remained two surgical patients (No. 31S and 45S in Table 11) for whom no satisfactory match could be found. One of these was an eighteen year old boy with severe hypertension of short duration, in whom there was no evidence of organic damage except for severe retinopathy with papilledema. This patient's response to sympathectomy was extremely satisfactory, but it must be emphasized that our failure to find a suitable control subject was entirely due to our inability to find a patient with similar preoperative clinical status in our control pool. The same is true of the other, an eleven year old boy with severe diastolic hypertension, in whom papilledema and definite evidence of renal and cerebral damage were present before the operation; in this

case the effect of sympathectomy was unsatisfactory, the patient having died fourteen months after the operation.

Use of Numerical Code in the Presentation of the Followup Results. Using the system of numerical grading described, the clinical status of each patient in the surgical and control series was reassessed at three intervals during the follow-up period, corresponding to the second, fifth and tenth anniversaries of the "operation." Since it was only in a small minority of instances that a complete follow-up examination had been performed during the anniversary month, a convention had to be established to govern grading by interpolation. The rule finally adopted was that only "level" interpolation would be permitted. For example, if an electrocardiogram had been taken at the end of the first postoperative year and another at the end of the third year, and if both were graded 2, it was considered justifiable, in the absence of any evidence from the history to suggest that some acute disturbance of cardiac function had occurred during the interval, to accept 2 as the electrocardiographic grade for the end of the second year. On the other hand, if the grades had been 0 at the end of the first year and 2 at the end of the third, there would have been no way of knowing when the change had occurred, and the electrocardiographic grade at the end of the second year would have been recorded as "-".

The postoperative blood pressure grades were based on the average of all "casual" readings made in the lying and sitting positions during a period beginning six months before, and ending six months after, the corresponding anniversary of the operation. Blood pressures recorded during periods of acute hypotension following catastrophes such as myocardial infarction or gastrointestinal hemorrhage were not used in calculating these averages, but readings were not excluded merely because they had been made while the patient was suffering from some chronic complication of hypertension, such as congestive failure or the late sequelae of a stroke. Whenever the readings from which the averages were calculated had been obtained during a period of effective treatment with hypotensive drugs, the corresponding blood pressure grades were underlined in order to call attention to the resulting possibility of error in evaluating the effect of the operation. Fortunately, this situation was encountered in only six instances, four in the surgical series and two in the control series.

Although the principal function of the postoperative grades was to indicate a patient's clinical status at the *end* of each follow-up period, an exception was made in order to enable the code to record the occurrence of complications such as myocardial infarction and cerebrovascular accident which take place as isolated events. Whenever such an event had occurred during a given follow-up interval (0 to 2, 2 to 5 or 5 to 10 years postoperatively), the appropriate severity

TEN YEAR FOLLOW-UP DATA ON HYPERTENSIVE PATIENTS TREATED BY THORACOLUMBAR SYMPATHECTOMY AS COMPARED WITH MATCHED CONTROLS TREATED SYMPTOMATICALLY Female Series

			Time Post-	opera- tively (mo.)							: :			611			10		96	16
		Death	-	Cause		***		::		::				CH	::		n		MI IM	СН
			Pa-	dema	0000	0000	900	0000	0000	0000	90-0	00-0	900	90-0	0000	1000	0000	0000	0000	1
	Retina	Grade 0,2,5,10 Yr.	-	athy c	0000	0000	0-00	0000	0000	0000	00-0	00-0	000	00-0	3-11	1000	0000	0000	000-	0-0
	R	0,2,		sels	1000	20-	0-00	1-12	1000	0000	2-21	3-32	0-2	2-03	2222	2222	2122	2222	2223	-2
			SG-	NPN	0000	0000	0000	0000	000	0000	00	-111	000	0000	2-0	110	1-10	00-00	1224	1-0
	Kidneys	Grade 0,2,5,10 Yr.	-	uria	0000	0000	0000	0000	0000	0000	0000	0010	1-11	0000	3010	3-1	1-10	1110	0-1123	0000
	X	0,2,		toms	0000	-0000	0000	0000	0000	0000	0000	=======================================	0-00	-000	0000	1110	1111	1211	0000-	0-00
	-	de 0 Yr.	T.	CVA	0000	-0000	0000	0000	0000	0000	0000	3111	0000	0000	0000	00000	0000	3000	-0000	24
	Brain	Grade 0,2,5,10 Yr.		ache	3011	3321	2122	2111	2110	2111	1000	3110	0000	0000	2121	3111	3011	2220	223- 1100	2-0000
			550		00-0	0-00	90-0	0-00	0000	111-	90-0	2-32	000	11-11	0000	2222	2-3	0000	22-	0000
	Heart	Grade 0,2,5,10 Yr.		azio	910	11-11	0-00	11-1	0-00	1-11	90-0	195	0-00		0000	2322	0-00	3332	2333	1
		0,2,	Symp	toms	0000	0000	0000	0000	0000	1113	==	2222	1122	000	0110	2222	1-12 112	2112	2224 0134	0000
Series			1	Fall	0000	-000	0-00	0000	0110	-110	1-21	0000	0-0	-0-0	1010	0000	0-10	-000	→ :	-0
Female Series		Grade 0,2,5,10 Yr.	Dias-	tolie	1001	300-	2-22	2112	2133	2111	3442	2210	3-3	333-	3222	$\frac{3132}{3-2}$	3-22	3322	3321	2232
Fe		0,5	Svs	tolie	1000	100-	2-22	2111	2123 3233	2222	3332	2110	$\frac{2-3}{22-1}$	2-3-	2111	$\frac{2121}{2-1}$	3-4	21111	323-	3-
	(mm. Hg)	nly)	rative	Minimum	108/60	110/70	120/70	110/60	110/70	110/78	112/70	120/58 125/82	$\frac{100}{70}$	90/60 $165/100$	140/100	$\frac{128}{64}$	120/80	112/70	128/80	110/80
	Blood Pressure (mm. Hg)	re Pressures O	Postoperative	Maximum	170/110	130/100	206/132 180/120	192/120 238/140	230/140 250/142	195/120 200/128	200/134 260/170	200/120 242/145	258/150 225/150	222/148 242/165	180/130 250/135	214/148 210/130	216/125 260/176	220/164 180/115	240/140 180/120	200/118
	Blo	Range (Lying and Sitting Pressures Only)	ative	Minimum	138/90	142/110	122/78	130/80	128/90 170/110*	158/96	140/86 150/100*	120/60	118/70	128/80 148/96 *	182/114* 174/106*	132/80 164/100*	150/100	144/94	144/80 138/100	132/82
	_	(Lying	Preoperative	Maximum	178/115	190/130	194/126 190/120	198/130	220/140 230/130	212/150 210/135	220/130 220/140	220/130 210/130	220/140 194/134	206/148 225/154	204/146 240/140	210/132 245/155	220/140 230/140	210/160 240/130	220/168	225/136
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AMERICAN JOURNAL OF MEDICINE

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170/105 142/100	130/70	150/100 126/86	130/60	160/80	160/80	160/98 220/120*	160/90 185/115*	164/100	170/110 180/110*	134/60 200/100	170/108 160/110	160/64 192/100	150/96 178/112*	200/126* 164/100	190/134 160/110*	162/120 180/120	166/106 150/100*	130/80 210/120	184/102 162/84	220/120 190/110*	154/80 180/100*	160/82 200/110*
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++	r.r.	++	+	1+	00	+4.	+1	+1	1+	11	++	1+	++	+1	a.+	1+	++	+	++	++	11	+4.
51.2	57.5	35.8	39.2	41.2	42.7	42.9	44.3	44.3	47.4	48.4	30.2	31.6	33.2	38.2	36.3	38.9	39.2	41.2	42.1 35.8	45.0	41.7	43.6
678 67C	68S‡	269 269	70S†	71S† 71C	72S 72C	73S† 73C	74S 74C	75S 75C	76S 76C	77S† 77C	78S 78C	79S 79C	80S 80C	81S 81C		83S 83C	84S 84C	85S 85C	86S 86C	878 87C	888 88C 88C	898 89C

TEN YEAR FOLLOW-UP DATA ON HYPERTENSIVE PATIENTS TREATED BY THORACOLUMBAR SYMPATHECTOMY AS COMPARED WITH MATCHED TABLE III (Continued)

CONTROLS TREATED SYMPTOMATICALLY

Female Series

Diase Pose Symple Size BCG Bead CVA Symple Pro- Figh Figh	Ganglia- Removed	Ganglia	Ganglia			Blood Pressure (mm. Hg)	Blood Pressure (mm. Hg)	slood Pressure (mm. Hg)	re (mm. Hg)	1	and the same of th				Heart		Brain	in		Kidneys		R	Retina			
Dissection Post Symp Size ECG Head CVA Symp Froin PSP. Vest New Popility Proposition Pro	Age liy tion (Lying and Sitting Pressures Only)	Fam. Dura. T-L. (Lying and Sitting His- of	T-L Rang (Lying and Sitting	Rang (Lying and Sitting	Rang (Lying and Sitting	(Lying and Sitting Pressures Only)	Range and Sitting Pressures Only)	g Pressures Only)	Only)		0,5	Grade 2,5,10 Y		0	Grade 2,5,10 Yr		Gra 0,2,5,1	de 0 Yr.	0,2	Grade,5,10 Yr		0,2,	irade 5,10 Yr	P.	Dea	q ₃
10 10 10 10 10 10 10 10	(yr.) 1st 2nd Preoperative Postoperative	(yr.) 1st 2nd Preoperative Postoperative	Preoperative Postoperative	Preoperative Postoperative	Preoperative Postoperative	Preoperative Postoperative	Postoperative			9		2								-	5	-	-			Time
333 00- 133 23-2 2-3 1-21 000 124 213 13-2 20-0 011 U 333-3 00- 1122 2222 2-3 12-1 000 111 1112 2222 000 000 111 1112 2222 000 000 111 111- 10-1 0-0-		Stage Maximum Minimum Maximum	Stage Maximum Minimum Maximum	Stage Maximum Minimum Maximum	Stage Maximum Minimum Maximum	Maximum Minimum Maximum	Maximum				tolic	tolic		Symp- toms		ECG	Head- ache		Symp- toms		NPN.			ra- pille- lema	Cause	opera- tively (mo.)
333- 332- 332- 332- 44 021- 322- 322- 322- 322- 322- 322- 322- 3	44.7 + 1 10-2 10-2 270/150 194/92 260/140 160/98 11.4 + 6 mo 240/140 172/96 * 245/170 190/100	+ 1 10-2 10-2 270/150 194/92 260/140 - 245/170	mo. 10-2 10-2 270/150 194/92 260/140 246/170	10-2 270/150 194/92 260/140 240/140 172/96 245/170	270/150 194/92 260/140 240/140 172/96 245/170	270/150 194/92 260/140 240/140 172/96 245/170	260/140		160/98		444	3333	-00	133	1	233	100	000	124	1	-	1		110	6	26
322- 3332 -10- -1124 011- 225- 2233 222- 334- 3234 322- 100- 100 10- 200 110- 200 110- 200 110- 322- 332- 332- 332- 332- 332- 332- 33	50.7 + 16 9-2 10-2 275/160 180/100 280/140 198/102 52.8 7 12 250/130 152/98 270/150 152/84	+ 16 9-2 10-2 275/160 180/100 280/140 198/102 250/130 122/98 270/150 152/84	9-2 10-2 275/160 180/100 280/140 198/102 250/130 152/98 270/150 152/84	10-2 275/160 180/100 280/140 198/102 250/130 152/98 270/150 152/84	255/160 180/100 280/140 198/102 250/130 152/98 270/150 152/84	255/160 180/100 280/140 198/102 250/130 152/98 270/150 152/84	280/140 198/102 270/150 152/84	198/102		4.61	444-	333-	021-	223-		2 2 2	-102	023-	222-	_		-		0000	* * * * * * * * * * * * * * * * * * * *	
4-1 0-1 1-3 2-2 3-2 2-2 3-3 3-4 1000 2020 11-1 1101 0000 322- 233- 600 HF 44- 0 1- 1- 2- 0- 1- 3- 2- 3- 3- 3- 9- 9- 41-0 01-0 1000 111 1000 1000 111 1000 1000 111 1000 1000 111 1000 111 1000 111 1000 111 1000 111 1000 111 1000 111 1000 111 1000 111 111 1000 111 111	300/154 182/100	+ 5 290/180 202/110 300/150 182/100	9-2 9-2 300/180 202/110 300/154 182/100 290/158 180/110* 285/150	9-2 300/180 202/110 300/154 182/100 290/158 180/110* 283/150 150/10**	300/180 202/110 300/154 182/100 290/158 180/110* 285/150 150/100	300/180 202/110 300/154 182/100 290/158 180/110* 285/150 150/100	300/154 182/100	182/100	-	3 400	433-	322-	-10-	-100		332-	-000	2001	-000						H	86
41-0 01-0 100 0-0 2-0 2-1 34 14 33 32 11 U 41-0 01-0 1100 0-00 3000 1000 1102 1000 1100 1000 111 10 0	190/120 188/136* 278/216 160/128	+ 2 mo. 8-2 266/178 190/120 -//- 270/180 188/136 278/216 160/128	mo. 8-2 266/178 190/120 -//- 270/180 188/136* 278/216 160/128	2 266/178 190/120 -///- 270/180 188/136* 278/216 160/128	266/178 190/120 -/- 278/216 160/128	190/120 188/136* 278/216 160/128	278/216 160/128	160/128		2 4 4	- 	44	0	1124		0-	3-	2020	Ξ;	-	0			9	HF.	92 4 days
421 -22 112 112 100 111 000 100 233 1202 1000 444 233 12- 23- 133 000 114 12- 12- 00- 0F 0F <td< td=""><td>100/50 205/120</td><td>+ 2 9-2 9-2 270/170 154/92 200/130 100/50 - 260/130 180/100 285/130 205/120</td><td>9-2 9-2 270/170 154/92 200/130 100/50 265/150 205/120</td><td>9-2 270/170 154/92 200/130 100/50 260/150 180/100 285/150 205/120</td><td>270/170 154/92 200/130 100/50 260/150 180/100 285/150 205/120</td><td>270/170 154/92 200/130 100/50 260/150 180/100 285/150 205/120</td><td>200/130 100/50 285/150 205/120</td><td>100/50 205/120</td><td></td><td>44</td><td>199</td><td>41-0</td><td>0-10</td><td>1000</td><td>-</td><td>00-0</td><td>3000</td><td>0001</td><td>1000</td><td></td><td>0</td><td></td><td></td><td>9</td><td></td><td>12</td></td<>	100/50 205/120	+ 2 9-2 9-2 270/170 154/92 200/130 100/50 - 260/130 180/100 285/130 205/120	9-2 9-2 270/170 154/92 200/130 100/50 265/150 205/120	9-2 270/170 154/92 200/130 100/50 260/150 180/100 285/150 205/120	270/170 154/92 200/130 100/50 260/150 180/100 285/150 205/120	270/170 154/92 200/130 100/50 260/150 180/100 285/150 205/120	200/130 100/50 285/150 205/120	100/50 205/120		44	199	41-0	0-10	1000	-	00-0	3000	0001	1000		0			9		12
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433- 021- 111- 0-0- 100- 323- 000- 111- 112- 2-2- 2-2- 1-0- 0-0- 114- 2233 2444 2233 0033 0000 U 4+ 1 2 0 222- 334 1-1 11	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	3 10-2 8-3 275/166 170/110 220/140 136/74 3 265/155 130/88 260/158 186/118	10-2 8-3 275/166 170/110 220/140 136/74 265/155 130/88 260/158 186/118	8-3 275/166 170/110 220/140 136/74 265/155 130/88 260/158 186/118	275/166 170/110 220/140 136/74 265/155 130/88 260/158 186/118	170/110 220/140 136/74 130/88 260/158 186/118	220/140 136/74 260/158 186/118	136/74		44	++	+4	-0	1.7		1 2	00 00	9 48	100						ICVD	30
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Nore: Abbrevations are the same as in Table II.

* Same significance as in Table II.

* Table II.

* Same significance as in Table II.

* Tab

testinal hemorrhage.

The grades of all items in the ten-year follow-up data of these five patients have been shown as "-" for the following reasons: Case 528; Patient known to have been alive and well at ten years and BP is said to have been manufatined within normal limits but patient deplication to co-operate in the formal ten-year follow-up examination. Cases 688, 918, 978 and 998; These patients were not seen at ten years but their blood pressures had returned to approximately the preoperative level prior to this time. Death occurred after the end of the ten-year period in all four cases, the cause of death and the time in months from the date of operation being as follows: 988, CH at 139 mo.; 978, CH at 139 mo.; 998, cause unknown, 138 mo.

grade was included in the data for that period, no matter at what point during the interval it had occurred. For example, if a patient had suffered a cerebrovascular accident of grade 2 severity at the end of the first postoperative year, the entry under CVA in the two-year data was recorded as 2, even though the patient might have made a complete functional recovery from the effects of the stroke before the end of the second year. On the other hand, a stroke of grade 4 severity, which had occurred between the second and fifth postoperative years, was indicated by the code in the five-year data only (in spite of the persistence of severe disability into the next follow-up interval) unless a second cerebrovascular accident had occurred between the fifth and tenth postoperative years.

When a given item in the clinical profile had been graded at each of the four standard intervals (preoperatively, and two, five and ten years postoperatively), it proved convenient to write the four grades in consecutive order as a single four digit number. For example, if cardiac symptoms were coded 0000, this would mean that the patient had been free of such symptoms throughout the entire period of observation. Similarly, a code entry of 4012 under systolic blood pressure would indicate that the pressure had been markedly elevated before the operation (grade 4, average "casual" systolic pressure over 230) and had been reduced to normal up to the end of the second year (grade 0), but had shown a slight tendency to increase during the next eight years (grade 1 at five years, grade 2 at ten years). The use of this system made it possible to condense the essential clinical data on any one patient for the entire period of observation into a series of fourteen four letter code numbers, one for each item in the clinical profile.

In dealing with the records of patients who had died before the end of the ten-year follow-up, a slight modification of this system was made in order to permit the code to indicate the patient's clinical status prior to death. For example, if a patient had died in the interval between the fifth and tenth anniversaries of the operation, strict adherence to the rules would have required that the final digits of all the code numbers for that patient be omitted, since no ten-year data were available. Under the modified rules, however, the fact that the patient had died was recorded as a separate item at the end of the code, and the fourth digit of each code number was used to describe the clinical situation during the final illness. Similarly, three digit code numbers were used for patients who had died between the second and fifth anniversaries of the operation, and two-digit numbers for those who did not survive two years.

RESULTS

Tables II and III present a summary of the clinical data on male and female patients,

FEBRUARY, 1960

respectively. In these tables the patients in the surgical series have been designated by case numbers 1S to 100S, the numbers from 1 to 50 having been assigned to the male patients and those from 51 to 100 to the females. Each control patient was given the same number as the surgical patient with which it was paired, the symbol C being substituted for S. The case numbers were assigned to the surgical patients in order of increasing preoperative systolic blood pressure grade, patients with the same systolic grade being listed in order of increasing diastolic grade, and those with the same grade for both systolic and diastolic pressure being arranged in order of increasing age.*

The five columns to the right of the one containing the case numbers give the "age at operation," the family history of hypertension, the known duration of the disease and the extent of the ganglionectomy performed on the surgical patients. Age is the only one of these items which was taken into consideration in selecting the control subjects, because family history was not thought to be of much prognostic significance and because information on duration of disease was not considered to be sufficiently accurate to provide a reliable basis for case matching.

The next four columns present two pairs of blood pressure readings which provide a rough indication of the range of spontaneous variation of the blood pressure during the preoperative and postoperative periods, respectively. The figures shown in the column headed "Blood Pressure—Preoperative—Maximum" represent the highest systolic and diastolic readings recorded under "casual" conditions during the six-month preoperative period. The corresponding "preoperative minimum" values are, in most cases, the lowest readings made under "resting" conditions in hospital, exclusive of pressures obtained during the sodium amytal sedation test and on the day following. Unfortunately, in four surgical patients and in more than half the control subjects, no "resting" pressures were available because all the initial investigation had been carried out on an outpatient basis. In order to avoid the necessity of leaving the "preoperative

* During the early stages of the investigation the cases were identified by a different set of serial numbers corresponding to the chronologic order of the date of "operation." When the final selection of the matched control subjects was made, the numbers used in Tables II and III were assigned in order that the arrangement of the cases in the tables might be based on some prognostically important characteristic of the disease.

minimum" column blank in all such cases, the lowest "casual" readings were entered whenever "resting" values were not available, such entries being identified by an asterisk to indicate that they are probably much higher than the values which would have been obtained if the patients had been admitted to hospital.* Fortunately, since only "casual" pressures were used in calculating the averages on which the numerical blood pressure grades were based, the absence of information on the minimum "resting" pressures in many control subjects did not introduce any error in the coded data.

The blood pressure readings listed under the headings "postoperative maximum" and "postoperative minimum" are the highest and lowest systolic and diastolic values recorded on any occasion during the ten-tear follow-up period, readings made during the first seven days after the second stage of the operation having been arbitrarily excluded. It was hoped that the difference between the preoperative and postoperative minimum pressures would serve as a rough index of the immediate blood pressure lowering effect of the operation, even though the corresponding data on the control subjects are subject to the limitations previously described.

The fourteen columns immediately to the right of those in which the maximum and minimum blood pressures are recorded contain the coded data on the various items in the clinical profile, while the two columns on the right hand side of the tables give the cause of death and the duration of survival of those patients who died before the end of the ten-year follow-up period. The abbreviations used in presenting this portion of the data are described in the footnotes to the tables.

Comparison of Preoperative Status of Patients in Surgical and Control Series. Table IV presents a tabular comparison of the preoperative status of the surgical and control patients in terms of each of the eighteen items for which data are given in Table II and III. The figures show that, for each sex as well as for the series as a whole, there was a satisfactory degree of similarity between the two groups with respect to each item in the preoperative clinical profile. It is interesting to note that the agreement in those

*The obvious solution to this problem would have been to provide separate columns for the minimum "casual" and minimum "resting" pressures in the preoperative and postoperative periods. This was done in the original data tables, but the extra columns were omitted from the final version in order to save space. items which were not used as a basis for the selection of the control subjects (family history, known duration of hypertension, maximum and minimum preoperative blood pressures and headache) was almost as close as it was in those on which the pairing was actually based. It seems fair to conclude, therefore, that there was no over-all, systematic bias with respect to "severity" of disease in the selection of the control subjects, even though detailed examination of the coded protocols in Tables II and III reveals many minor discrepancies between individual propositi and their controls.

The variability of the blood pressure during the "preoperative" period is one aspect of the data which deserves additional comment, because it is an important limiting factor in the precision which can be attained in evaluating the long term effect of the operation in lowering blood pressure. If an "index of blood pressure variability" is arbitrarily defined as the difference between the maximum "casual" and minimum "resting" pressures, expressed as a percentage of the former, the figures given in Table IV for the average preoperative maximum and minimum pressures of the surgical patients correspond to indices of variability of about 33 per cent for the systolic pressure and 38 per cent for the diastolic. There was no significant difference in blood pressure variability, as measured by this index, between men and women, or between surgically treated and control patients, provided the data from patients in whom "resting" blood pressures were not available were excluded.

The validity of this method of calculating the blood pressure "variability" of a given patient is largely a function of the number of individual casual and resting pressures which can be obtained from the patient's record, the value of the index of variability tending to increase as the number of readings on which it is based increases. However, experience has shown that an index based on ten casual pressures taken during a six-month period and twenty-five resting pressures taken at the rate of three or four readings daily during a seven- to ten-day stay in the hospital, is not likely to be changed significantly by the accumulation of more data. Unfortunately, the number of readings available was much fewer than this in the majority of cases, especially in the surgical series; therefore, the indices of variability calculated from the data given in Tables II and III must be considered merely as rough approximations which under-

Table IV
COMPARISON OF PREOPERATIVE STATUS OF SURGICAL AND CONTROL PATIENTS*

Proposative Findings	M	ales	Fen	nales	Т	otal
Preoperative Findings	Surgical	Control	Surgical	Control	Surgical	Control
Average age (yr.). Average duration of hypertension (yr.). Average maximum preoperative blood pressure (mm. Hg) Average minimum preoperative blood pressure (mm. Hg)	39.4 3.9 229/152 152/92	39.2 4.2 232/149 172†/106	39.8 5.8 239/151 159/94	39.7 4.4 244/149 168†/103	39.6 4.9 234/151 156/93	39.5 4.3 238/149 170†/104
Family history of hypertension						
++	7	6	1	2	8	8
+	18	20	27	26	45	46
	6 17	5 17	6	8	12 33	13 31
	48	48	50	50	98	98
Systolic blood pressure						
Grade 0	0	0	0	0	0	0
1	2	0	2	1	4	1
2	22	22	12	10	34	32
3	17	14	23	25	40	39
4	7	12	13	14	20	26
	48	48	50	50	98	98
Diastolic blood pressure						
Grade 0	0	0	0	0	0	0
1	0	0	1	1	1	1
2	9	11	10	8	19	19
3	22	19	21	20	43	39
4	17	18	• 18	21	35	39
	48	48	50	50	98	98
Cardiac symptoms						
Grade 0	26	33	16	21	42	54
1	12	6	26	23	38	29
2	5	7	8	4	13	11
3, , , ,	5	2	0	2	5	4
4	0	0	0	0	0	0
	48	48	50	50	98	98
Heart size	4.5		20			40
Grade 0	15	6	22	12	37	18
1	19	17	13	9	32	26
2	12	16	13	21	25	37 5
34	0	0	0	0	0	0
				0	- 0	
	48	43	49	43	97	86
Electrocardiographic abnormalities	22	22	10	10	42	44
Grade 0	23	23	19	18	42	41
1	7 7	11	20	17	37	28
2	1	8	9	12	16	20
4	0	0	0	0	0	0
	48	43	49	48	97	91

Table iv (Continued)

COMPARISON OF PREOPERATIVE STATUS OF SURGICAL AND CONTROL PATIENTS*

	M	ales	Fen	nales	То	otal
Preoperative Findings	Surgical	Control	Surgical	Control	Surgical	Contro
Headache						
Grade 0	23	20	15	13	38	33
1	9	13	5	13	14	26
2	9	11	21	18	30	29
3	5	2	8	4	13	6
4	2	2	0	2	2	4
	48	48	49	50	97	98
Cerebrovascular accidents						
Grade 0	37	38	37	37	74	75
1	1	5	3	4	4	9
2	5	1	6	5	11	6
3	5	4	4	4	9	8
4	0	0	0	0	0	0
	48	48	50	50	98	98
Renal symptoms						
Grade 0	38	39	29	29	67	68
1	8	6	17	18	25	24
2	2	3	4	3	6	6
4	0	0	0	0	0	0
***************************************				-		
	48	48	50	50	98	98
Proteinuria	28	32	22	26	50	58
Grade 0	10	9	21	16	31	25
2	7	5	4	6	11	11
3	3	1	3	2	6	3
4	0	1	0	0	0	1
	48	48	50	50	98	98
Renal function						
Grade 0	35	32	26	31	61	63
1	8	11	17	14	25	25
2	5	4	6	3	11	7
4	0	0	0	0	0	0
	48	47	49	48	97	95
-	-	-				
Retinal vessels Grade 0	6	8	6	4	12	12
1	15	13	12	12	27	25
2	12	14	23	20	35	34
3	9	9	5	9	14	18
4	3	3	1	1	4	4
	45	47	47	46	92	93

Table IV (Continued)

COMPARISON OF PREOPERATIVE STATUS OF SURGICAL AND CONTROL PATIENTS*

	Ma	ales	Fen	nales	То	otal
Preoperative Findings	Surgical	Control	Surgical	Control	Surgical	Control
Retinopathy						
Grade 0	33	31	35	32	68	63
1	5	7	9	5	14	12
2	4	5	4	4	8	9
3	5	3	2	4	7	7
4	1	1	0	1	1	2
	48	47	50	46	98	93
Papilledema						
Grade 0	38	37	45	41	83	78
1	4	5	3	4	7	9
2	3	3	0	0	3	3
3	3	1	2	1	5	2
	0	1	0	0	0	1
	48	47	50	46	98	93

* Data on the two surgical patients for whom suitable control subjects could not be found have been omitted from this table.

† See text for differences between circumstances in which minimum blood pressures of surgical and control patients were taken.

estimate the true values by an amount which varies from patient to patient. Nevertheless, the range and distribution of these indices suggest that a considerable degree of lability of blood pressure is a basic characteristic of most patients with hypertension who are considered suitable candidates for sympathectomy. Moreover, this variability appears to be little affected by the average height of the blood pressure or by the degree of organic damage as indicated by the cardiac, cerebral, renal and retinal gradings.

In the surgically treated males, for example, the index of variability averaged 31 per cent systolic and 40 per cent diastolic in patients whose preoperative systolic blood pressures were graded 1 or 2, as compared to 38 per cent systolic and 39 per cent diastolic in those graded 3 or 4. Similarly, when the series was divided, as will be described, into three groups on the basis of increasing "severity" of organic complications, the corresponding indices of variability were as follows: group A, 32 and 40 per cent; group B, 34 and 37 per cent; and group C, 35 and 43 per cent.

Although, in order to save space, the minimum casual pressures have not been given in Tables II and III (except in those cases in which

no resting pressures were available), the original protocols show that the variability of the casual pressures accounts for about half of the total variability which, according to our definition, is measured in terms of the difference between the highest casual and the lowest resting pressure. The extent to which the inherent variability of the blood pressure complicates the assessment of antihypertensive therapy is illustrated in one of its most extreme forms by the record of Case 22S, a forty-three year old man who came to the clinic because of visual symptoms caused by severe hypertensive retinopathy with early papilledema. During a six-week period of investigation as an outpatient his casual blood pressure varied between 220/160 and 155/115 mm. Hg (index of casual variability 29 per cent systolic, 28 per cent diastolic), but after admission to hospital his resting blood pressure was recorded as low as 102/50 (index of variability 54 per cent systolic, 69 per cent diastolic). On a preoperative "posture and cold" blood pressure test performed three days after admission, the average readings were 110/80, 116/84, and 112/78 in the lying, sitting and standing positions, respectively, and 116/82 after one hand

had been immersed in ice water for one minute. Thus, on the basis of this standardized test, which has often been used as a basis for the evaluation of the effect of sympathectomy on blood pressure, this "severely hypertensive" patient would have been classified as perfectly normotensive while awaiting sympathectomy.

Comparison of Preoperative Status of Male and Female Patients. When the figures given in Table IV were used to compare the preoperative status of the patients on the basis of sex, only a few

significant differences were found.

Systolic blood pressure showed a definite tendency to be higher in women than in men. In the surgical series, for example, preoperative systolic grades of 3 or 4 were found in thirty-six of fifty women but in only twenty-four of forty-eight men ($X^2 = 4.1$; P < 0.05), corresponding figures for the control series being thirty-nine of fifty and twenty-two of forty-eight, respectively, $(X^2 = 5.2; P < 0.03)$. This difference was also reflected in the average maximum preoperative systolic blood pressure, which was 239 in the women and 229 in the men. There was no comparable sex difference with respect to the preoperative diastolic pressure, however, either in the distribution of grades or in the average maximum values.

Cardiac symptoms of grade 1 severity were much more common in women than in men (P < 0.01), but it is difficult to attach much prognostic significance to dyspnea of such slight degree which, in many instances, seems to have been due to obesity or to habitual lack of physical exercise, rather than to genuine impairment of myocardial reserve. Moreover, the sex difference with respect to minor abnormalities of heart size was in the opposite direction, the incidence of grade 1 changes being slightly more frequent in men in both the surgical and the control series (P = 0.05). The slightly higher frequency in women of grade 1 and 2 changes in the electrocardiogram is not statistically significant on the basis of the X2 test. It seems justifiable, therefore, to include that there was no significant difference between the two sexes with respect to overall preoperative cardiac status.

Headache was somewhat more common in women (P = 0.03), but cerebrovascular accident occurred with approximately the same frequency in the two sexes.

Renal abnormalities of all three types showed a slight but consistent tendency to occur more frequently in women than in men, but this was largely confined to abnormalities of the lowest grade of severity.

Abnormalities of the retinal vessels and retinopathy were more or less equally common in the two sexes, but papilledema occurred with a frequency which showed a higher male/female ratio than any other preoperative finding, namely, ten of forty-eight in men (or twelve of fifty if the two unmatched surgical cases are included) as compared with five of fifty in women. This difference is probably partly due to a higher incidence of papilledema in men with hypertension generally, and partly to the greater tendency of men to postpone presenting themselves for treatment until serious symptoms have made their appearance.

Comparison of Postoperative Course of Surgically Treated and Control Subjects. In evaluating the effect of the operation on the course of the disease it is obviously desirable to examine the possibility that the magnitude of the effect may vary with the stage of the disease at which the operation is performed. The crucial prognostic importance of the presence of organic complications has been emphasized by many authors, especially by Griep et al. [15] in their report on a seven to eleven-year follow-up study of 117 untreated patients whose age, blood pressure levels and general clinical status at the start of the investigation would have made them acceptable candidates for sympathectomy. They divided their cases into two groups on the basis of the presence or absence of certain specified hypertensive "complications" (abnormal electrocardiograms, cardiac enlargement, cerebrovascular accident and focal encephalopathy), and showed that the mortality rate was strikingly higher in the patients in whom one or more of the "complications" was present at the start of the follow-up period.

In order to take cognizance of "complications" other than those listed by Griep and his coworkers, and to permit our results to reflect the well known adverse prognostic significance of papilledema, we have expanded the definition of complications to include cerebrovascular accident, retinopathy or papilledema of any grade, and cardiac symptoms, cardiac enlargement, electrocardiographic abnormalities, renal symptoms, proteinuria or impairment of renal function of grade 2 or more.* Using this defini-

^{*} The presence of a grade 1 abnormality in each of the six items in the cardiac and renal panels was also accepted as evidence of complication.

tion, we have divided our cases into three groups as follows: group A, no preoperative complications; group B, one or more complications other than papilledema; and group C, papilledema with or without other complications.

In spite of the objections which we have raised to the use of such arbitrarily defined severity groupings as the sole basis for the comparison of one group of cases with another, we believe that such subdivisions may provide a useful basis for comparison of groups of cases, provided each patient in one group has been individually matched with a patient in the other group with respect to each aspect of the clinical profile. The use of such preoperative groupings is also of value in comparing the effects of the operation in any two subdivisions of the clinical material, males and females for example, when the incidence of complications in the two subdivisions is markedly dissimilar. Accordingly, in the analysis which follows, the cases in each of the two main series, surgical and control, have been subdivided into six sections, namely, group A males and females, group B males and females, and group C males and females.

Table v has been prepared from the data in Tables II and III in order to facilitate the comparison of the frequency with which favorable and unfavorable changes in each item in the clinical profile have occurred in the surgical and control patients in each of the six groups at the end of the follow-up period. In calculating the figures given in Table v, the end of the follow-up period was defined as the end of the tenth postoperative year in the case of the survivors, or the time of death in those who did not survive ten years, provided that the situation at the time of the final illness was a matter of record, or could be deduced from the available evidence with reasonable accuracy.

The decision regarding the magnitude of the change in preoperative status which should be accepted as "significant" presents many obvious difficulties; therefore, it was necessary to adopt a series of arbitrary definitions which could be applied to the coded data with a minimum of ambiguity. For the purposes of Table v a significant change was defined as either (1) a change of two or more grades in any item in the clinical profile; such a change in either systolic or diastolic pressure being accepted as a significant change in blood pressure, or (2) a change from 0 to 1 or vice versa in the grading of cerebrovascular accident, retinopathy or papilledema,

or (3) a change from 3 to 4 in the grading of cardiac symptoms or electrocardiographic abnormalities. In dealing with cerebrovascular accident the central problem was one of "recurrence" rather than "improvement," since it would obviously have been meaningless to describe a patient who had had a cerebrovascular accident in the preoperative period and who suffered one or more recurrences postoperatively as having been improved, merely because the stroke which occurred during the postoperative period was less severe than the preoperative episode.

The entries in the various columns in Table v have been shown as fractions in which the denominator represents the total number of patients in whom it would have been possible for a significant change to have been reflected by the code, and the numerator gives the number of patients in which such a change did, in fact, occur. For example, the first entry in Table v under "Preoperative Group A, Male, Surgical" opposite "Blood Pressure: Lower" is 4/11; this means that a decrease of the required two grades persisted to the end of the followup period in four of the eleven patients in this subdivision of the series. If there had been any patients in this subdivision in whom the preoperative blood pressure had been graded 1, such patients would not have been counted in arriving at the denominator because, even if their blood pressures had been reduced to normal, this would not have been classed as a significant decrease under the convention which requires a reduction of at least two grades. Similarly, by virtue of the inherent limitations of any system of grading based on the 0 to 4 scale, it would be impossible for a patient who was graded 4 in any item (or 3 in an item for which a change of two grades is the minimum for significance) to be recorded as having become "significantly worse" during the postoperative period; such a patient would not be counted in the denominator since, in effect, he would not be part of the "population at risk." Another factor which reduced the denominators of many of the fractions in Table v was the occurrence of gaps in the postoperative record of the corresponding items in the clinical profile, such gaps being somewhat more frequent in the surgical series than in the controls.

In spite of all these limitations, it is considered that the type of analysis presented in Table v summarizes most of the information which is

FREQUENCY OF IMPROVEMENT AND DETERIORATION IN INDIVIDUAL ITEMS OF CLINICAL PROFILE DURING TEN-YEAR FOLLOW-UP PERIOD Comparison on Basis of Method of Treatment, Sex and Preoperative Status

	Preope	rative	Group A	Preoperative Group A (no complications*)	nplicati	ons*)	(eom)	Preo	perative is other	Group than p	Preoperative Group B (complications other than papilledema)	na)	Preo	perative	Group	C (papi	Preoperative Group C (papilledema†)	9			All Cases	68	
Data	Male	de	Female	ale	Total	la	Male	9	Female	ale	Total	7	Male	9	Female	le le	Total		Male	-	Female	9	Total
	Sur- gical	Com- trol	Sur- gical	Con- trol	Sur- gieal	Con-	Sur- gical	Con- trol	Sur- gical	Con- trol	Sur- gical	Con-	Sur- gical	Con- trol	Sur- gical	Con- trol	Sur- C	Con- trol g	Sur- gical	Con- trol	Sur- gical	Con- trol	Sur- Con-
No. of cases.	=	14	20	17	31	31	27	21	25	28	52	52	10	10	20	10	15	15	89	90	000	20	98 88
Lower Lower Higher	4/11	0/14	6/19	2/16	10/30	2/30	9/23	0/24	7/22 0/6	3/27	16/45	3/51 0/15	1/10	0/8	1/3	0/4	2/13 0	0/12 1	14/44 2/22	0/46 1	14/44 0/16	5/47 28/0/12 2/	/88 5/93 //38 1/37
Better Worse	3/9	4/11	1/18	3/16	4/27	7/27	9/20	0/7	0/5 8/16	7/25	2/12	0/11	6/8	3/8	0/3	0/1	0/3 6/11 8	0/3	2/8	0/9	9/37	0/5	2/15 27/74 33/77
Decreased Increased	.2/0	4/11	6/14	3/13	0/21	7/24	0/6	0/6	0/3	0/11	0/8	0/17	0/2	0/1 2/5	0/1	0/2	0/1 (0/4 5	0/1	0/6	0/4	0,4 0	0/11 5/37	0/10 2/50 13/67
Better Worse	2/8	3/12	1/14	3/8	3/22	6/20	1/9 2/16	0/13	0/6	0/16	1/15	0/29 8/34	0/1	0/4	0/1	0/1	0/2 (0/4	1/10 5/28	0/17	9/28	0/16	1/17 0/33 8/56 16/62
Better.	1/2	1/2 0/12	5/11 0/17	5/7	6/13	6/9	1/2 0/15	3/7	3/5	4/12	4/7 0/23	7/19 2/40	3/4	0/4	2/2	1/2 0/3	5/6	9/0	5/8	4/13	10/18	10/21 1	15/26 14/34 1/65 2/76
rectorvascular accuent: No recurrence postoperatively One or more recurrences. First episode postoperatively.	1/9	2/13	3/19	5/17	4/28	7/30	3/10 7/10 5/14	3/9 6/9 4/14	5/12 7/12 2/8	8/11 3/11 2/15	8/22 14/22 7/22	11/20 9/20 6/29	1/1	0/1 1/1 2/6	1/1 0/1 2/3	1/1 0/1 1/3	1/2 1/2 6/10	1/2 1/2 3/9 1	3/11 8/11 10/30	3/10 7/10 8/33	6/13	9/12 3/12 8/35	9/24 12/22 15/24 10/22 17/60 16/68
Nettar symptoms: Better Worse	2/9	1/13	0/17	0/15	2/26	1/18	0/1 2/16	0/1	0/1 3/12	7/25	0/2 28/28	0/1	2/5	0/3	0/2	0/1	2/7	0/3	0/1 6/30	0/3	0/1 3/31	0/1 8/44	0/2 0/4 9/61 22/88
Peressed Deressed Increased	1/8	1/13	0/15	1/16	1/23	2/29	2/4	0/1 4/18	1/4	0/5 4/26	3/8	0/6	0/3	0/5	0/2	1/1	0/3	1/6	2/7	9/8	1/4	1/6 5/43	3/11 1/12 3/56 14/80
Rehal unction: Better Vorse	4/9	1/13	12/12	2/15	6/21	3/28	3/14	10/1	1/2 3/12	0/2	1/4 6/26	0/3	0/2	8/8	1/3	1/3	0/2 3/10	9/1	0/4	19/39	1/2 6/27	10/42	1/6 0/6 15/57 29/81
Retinal vessels: Better Worse	2/2	0/2 2/13	1/7 2/15	0/5	3/9	0/7 3/26	3/6 0/15	0/13 3/14	9/0	0/12	3/11 0/21	0/25	2/8	0/7	1/2	0/3	3/10	0/10	7/16	0/22 5/28	2/14	0/20	9/30
Retinopathy: Better Worse.	00/	1/17	0/16	6/16	2/24	7/33	5/5	1/7	2/2	2/4 6/19	7/7 2/25	3/11	2/5	0/7	0/5	1/3	4/7	1/10	7/10	1/14	1/27	3/7	11/12 4/21 4/54 19/75
Fapuledema: Better Worse	8/0	1/17	0/17	1/15	0/25	2/32	0/17	18	1/10	4/21	1/27	8/39	9/0	0/6	2/2	2/3	8/0	2/9	5/7	0/6 5/40	2/2	2/3	1/60
Dead at ten years: No.	18 23	2.4	102	28 33	± 55	16	13	14	22.8	114 50	48	28	80 S	100	909	90	73	13	48	26	17	20 40	40
Mean surival time (mo.)	114	06	39	82	20	88	52	46	53	54	52	52	62	14	18	13	21	**	47	39	44	23	46
Survivors: Incapacitated/Total	0/0	1/19	0/18	0.114	0.797	1 100	3 7 5 4	01/0	1110	1111	9 /97	2 /0.4	0.0		0/0	6/0	0.74	6/0	1,98	9 700	1 100	06/1	02/6

* For the purpose of this table the term "complications" includes papilledema, retinopathy or cerebrovascular accident of any grade, and any item in the cardiac or renal panels which is graded 2 or more.

relevant to the principal questions which controlled follow-up studies are designed to answer, namely, (1) how effective is the operation in causing amelioration, or in preventing recurrence, of those manifestations of the disease which were present in relatively severe degree preoperatively? and (2) how effective is the operation in preventing the occurrence or progression of various types of organic damage in patients who were free, or relatively free, of such damage preoperatively? In the sections which follow each of the items in the clinical profile will be discussed in turn with these two questions in mind.

Blood Pressure. The figures in the blood pressure section of Table v show that significant decreases in blood pressure, as herein defined, occurred in about one-third of the surgically treated patients, the proportions being exactly the same in males and females, and approximately the same in each of the preoperative clinical categories. In the control patients, on the other hand, significant decreases in blood pressure occurred in only five cases, and in all but one of these the blood pressure reduction was caused by, or associated with, various unfavorable clinical developments. This was also true of many of the surgically treated patients in whom significant reductions of blood pressure were recorded. For example, in Cases 44S and 78S a period of significant blood pressure reduction lasting several years was followed by a major cerebrovascular accident which was totally disabling in the former and fatal in the latter. In Cases 9S and 58S, in which both patients had had cerebrovascular accidents in the preoperative period, the sequence of events suggested that multiple strokes which occurred during the postoperative period may have been the cause of the observed decreases in blood pressure. In Case 95S the evidence suggests that the decline in blood pressure may have been partly the result of progressive cardiac failure from which the patient eventually died. In Case 29S the normal blood pressure at ten years may have been due, at least in part, to the fact that this patient had spent the previous four years undergoing treatment in a tuberculosis sanatorium, the blood pressure when tuberculosis was first discovered having been almost as high as it had been during the preoperative period.

Case 25S is another example of significant blood pressure reduction at ten years which was not the direct result of the operation; in this pa-

tient the blood pressure, which had returned to the preoperative level after the first two years, had been reduced to nearly normal levels by a period of intensive antihypertensive drug therapy in the tenth postoperative year. When these and other questionable cases were excluded there remained twenty surgically treated patients (ten men and ten women) and one control subject in whom an apparently genuine blood pressure reduction had occurred and had been associated with an apparently "favorable" clinical outcome, the patients being alive and reasonably well at the end of ten years. The fact that these favorable results occurred equally frequently in males and females in the surgical series is not in accord with the widely held opinion that the operation is more effective in women than in men. The low incidence of significant "spontaneous" reductions in blood pressure in control patients is in agreement with the observations of Griep and his co-workers [15].

Since the grades on which the analysis in Table v is based were derived from the average blood pressure levels at various follow-up intervals, it is of interest to consider the effect of sympathectomy on the blood pressure from a somewhat different point of view, namely, the ability of the operation to reduce the maximum levels to which the blood pressure may rise in response to minor stresses, such as those which are commonly associated with the measurement of the casual blood pressure during the ordinary clinical examination. Inspection of the maximum blood pressure data on the surgical patients in Table II and III reveals many instances in which markedly elevated individual blood pressure readings have been recorded during the postoperative period, even though a significant decrease in blood pressure grade has occurred. In Cases 78S and 94S, for example, the diastolic grade was reduced from 4 to 0 even though the maximum pressures recorded during the postoperative period were 200/120 and 200/130 mm. Hg, respectively. Also, in Case 72S, a significant decrease in diastolic grade from 3 to 1 was recorded in spite of the fact that the maximum preoperative and postoperative pressures were almost equal, namely, 230/134 and 235/125 mm. Hg. Such discrepancies may arise whenever the maximum blood pressures occur at times outside the periods which are used as the basis for calculating the two-, five- and ten-year grades.

We recognize the anomaly of assigning a

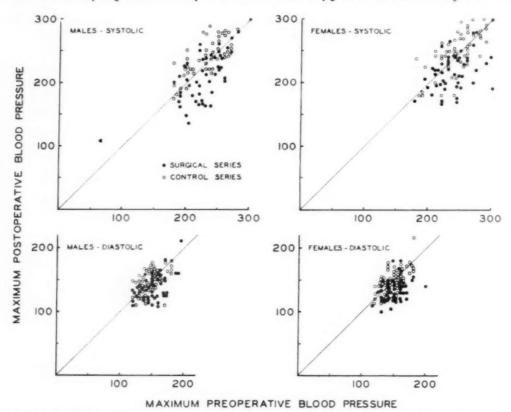


Fig. 1. Scatter diagrams showing the relation between the maximum preoperative and maximum postoperative blood pressures of each patient in the surgical and control groups. Black dots = surgical patients. Open circles = control subjects.

blood pressure grade of 0 to a patient in whom readings of the order of 200/130 have been recorded by reliable observers on one or more occasions, no matter how small a proportion of the available readings may have been elevated to this extent. Nevertheless, having adopted a set of rules to govern the grading of the data, one has no alternative but to follow them to the letter, otherwise an uncontrollable subjective element may be introduced into the grading, and this may well rob the system of any statistical significance which it might otherwise be capable of achieving. However, by supplementing the numerical blood pressure grades by the presentation of actual figures for the observed maximum and minimum values, anomalous behavior of the blood pressure can be indicated clearly. The occurrence from time to time of these relatively high peak pressures in patients whose average level is normal or nearly normal may well be an important factor in the explanation of the discrepancies which are often observed between the effect of the operation on blood pressure and its over-all clinical result.

The relationship between the preoperative

and postoperative maximum pressures in both series is illustrated in the scatter diagrams of Figure 1. Although the expected random variations in both directions are evident, the data for thè control series show no clear-cut tendency for the highest pressures during the postoperative period to differ systematically from the highest values recorded during the preoperative period. Most of the points lie within 30 mm. systolic and 20 mm. diastolic of the diagonal lines corresponding to equality of the preoperative and postoperative maximum pressures. The points representing the surgically treated patients are distributed in a somewhat similar fashion, but with the important exception that about onethird of the postoperative maximum pressures are more than 30 mm. systolic or 20 mm. diastolic below the corresponding preoperative values.

These relationships are summarized in Table vi, which shows that the average difference between the preoperative and postoperative maximum blood pressures of the surgical patients was a decrease of 21 mm. systolic and 15 mm. diastolic, as compared with an increase

Table VI
COMPARISON OF MAXIMUM PREOPERATIVE AND MAXIMUM POSTOPERATIVE BLOOD PRESSURES

Fr. P.	Ma	les	Fem	ales	To	tal
Findings	Surgical	Control	Surgical	Control	Surgical	Control
No. of cases	48 229/152	48 232/149	50 239/151	50 244/149	98 234/151	98 238/149
Average maximum postoperative blood pressure		241/148	217/135	249/151	213/136	245/149
Difference (postoperative-preoperative)	-20/-14	,	-22/-16		-21/-15	, , , , , , , , , , , , , , , , , , , ,
No. of cases in which maximum postoperative blood pressure was <i>lower</i> than maximum preoperative:						
By more than 30 mm. systolic	14	0	16	4	30	4
By more than 20 mm. diastolic	15	2	19	2	34	4
No. of cases in which maximum postoperative blood pressure was <i>higher</i> than maximum preoperative:						
By more than 30 mm. systolic	2	6	2	8	4	14
By more than 20 mm. diastolic	0	5	1	4	1	9

of 7 mm. in the systolic pressure and no change in the diastolic pressure in the controls. As far as sex differences are concerned, the data on the maximum pressures do not indicate that the effect of the operation in respect to lowering the blood pressure was greater in females than in males; this is in accord with the results obtained by analysis of the average blood pressure grades.

The fact that there were only two surgical patients in whom the maximum postoperative pressures exceeded the corresponding preoperative readings by more than 30 mm. systolic or 20 mm. diastolic deserves to be emphasized, but it is also of considerable interest to note that such a difference occurred in less than onequarter of the control subjects. This tendency for the blood pressure of patients with established hypertension to vary widely, but to remain within more or less constant upper and lower limits throughout most of the course of the disease, has been referred to as the "plateau effect" in a paper in which the phenomenon is illustrated by means of long term graphs of blood pressure variations in patients suffering from hypertension of various degrees of severity [16]. This point has also been emphasized by Griep et al. [15] who presented a scatter diagram, based on the diastolic pressures of medically treated patients, which is strikingly similar to the one shown in Figure 1. In their series of sixty-seven patients (forty-three survivors and twenty-four who died), the blood pressure was taken under casual conditions on a

single occasion at the beginning of a seven- to eleven-year follow-up period and again at the end of this interval or shortly before death, and the median change in diastolic pressure was found to be a decrease of 2 mm.

The figures for minimum postoperative blood pressure given in Tables II and III confirm the ability of sympathectomy to produce a marked fall in blood pressure in the majority of patients in the immediate postoperative period. Although it was recognized that such reductions of blood pressure, even when of relatively short duration, may produce certain beneficial results, it was considered reasonable, from the standpoint of a ten-year follow-up, to adopt the end of the second postoperative year as the first point for which data were given in the numerical code.

Orthostatic Hypotension. The blood pressures on which the foregoing discussion was based were all taken under casual conditions with the patient in the lying or sitting position. The blood pressures of the control patients were seldom taken in the standing position since none of them had received ganglionic blocking agents or other drugs known to be capable of producing orthostatic hypotension, but in the surgically treated patients, standing blood pressures were taken frequently as a check on the degree of orthostatic hypotension resulting from the operation. Since it is generally believed that the decrease in blood pressure which occurs when the sympathectomized patient stands is responsible for many of the beneficial effects of the

212

TABLE VII
FREQUENCY OF ORTHOSTATIC HYPOTENSION IN
SURGICAL SERIES

		nts Who			nts Who	
Grade	Males	Fe- males	Total	Males	Fe- males	Total
	Orthosta	tic Hypo	tension a	t Two Y	ears	
0	11	12	23	6	4	10
1	9	9	18	7	3	10
2	3	5	8	3	4	7
3-4	0	0	0	0	0	0
	23	26	49	16	11	27
	Orthostal	tic Hypo	tension a	t Ten Ye	ears	
0	14	19	33			
1	6	3	9			
2-4	0	0	0			
	20	22	42			

operation, data on the degree of orthostatic hypotension are given in the column headed "Postural Fall" in Tables II and III. It should be noted, however, that the striking orthostatic hypotension which often occurs during the first few weeks or months of the postoperative period was not reflected in the coded data, because the first postoperative grade corresponds to the end of the second postoperative year, by which time the more severe degree of orthostatic hypotension had disappeared in the great majority of patients.

The data on orthostatic hypotension are summarized in Table vII which shows that at the end of two years less than 60 per cent of the patients for whom adequate information was available had a fall of blood pressure in the standing position of 5 per cent or more. Table vII also shows that the incidence of orthostatic hypotension at two years was slightly higher in the patients who died before the end of the tenyear follow-up period than in those who survived this interval. Although this difference is not statistically significant, the results do not offer any support for the belief that the occurrence of orthostatic hypotension in the early years of the postoperative period is a favorable sign from

the standpoint of long term prognosis. The decrease in the frequency of orthostatic hypotension with time, on the other hand, is quite definite, the difference between the figures for the survivors at two years and at ten years being statistically significant at the 1 per cent level.

Cardiac Status. The figures given in Table v for the three items in the cardiac panel (symptoms, heart size and electrocardiogram) are sufficiently similar to permit them to be considered as a group. In the control series, for example, there was not a single instance in which a preoperative grade of 2 or more in any of the three cardiac items had decreased "significantly" at the end of the postoperative period. Even in the surgically treated group such improvement was distinctly unusual, cardiac symptoms having decreased 2 or more grades in two patients and electrocardiographic abnormalities having decreased to this extent in only one. Looking at the problem from the opposite point of view, namely, the frequency with which deterioration of cardiac status occurred, there is a consistent difference in favor of the surgically treated patients in each of the three items, the difference with respect to heart size being significant at the 5 per cent level.

It is difficult to compare these data regarding improvement in the electrocardiogram with those of Bridges and his co-workers [17] who found some improvement in the amplitude of the T waves in leads I and II in 11 per cent and 16 per cent, respectively, of 144 patients studied one year after thoracolumbar sympathectomy. The difference in the length of follow-up is probably one important factor, the other being the fact that our criterion of significant improvement was probably more stringent than theirs, since the mean increase in the amplitude of upright T waves in leads I and II in their series was only 1 mm.

Headache. Improvement of 2 or more grades in the severity of headache occurred in fifteen of twenty-six surgical patients (58 per cent) and in fourteen of thirty-four control subjects (41 per cent). This difference lacks statistical significance, but the relatively high incidence of spontaneous relief of headache in the control subjects, in the absence of a significant reduction in blood pressure, is in accord with the generally held view that the severity of most of the headaches of which hypertensive patients complain is poorly correlated with the height of

the blood pressure [18]. This is certainly true of headaches of moderate severity in which psychogenic factors are of major importance, but genuine hypertensive headache of grade 4 severity, although relatively uncommon, is of serious prognostic significance. All six patients in this series in whom headache of this degree of severity had been present before the operation died before the end of the follow-up period, the average survival time having been only eight months. However, the inherently non-progressive nature of the headaches which occur in the majority of hypertensive patients is reflected in the small number of cases in which the severity increased by 2 or more grades during the tenyear period, such an increase having been observed in only one patient in the surgical series and in only two of the control subjects.

Cerebrovascular Accidents. There is urgent need for more accurate data on the effect of sympathectomy on the prognosis of hypertensive patients with respect to cerebrovascular accidents, because the operation is often recommended to, and accepted by, such patients in the hope that strokes can be prevented or postponed. Table v shows that, among patients who had suffered a cerebrovascular accident during the preoperative period, the incidence of one or more recurrences during the ten-year followup interval was 62 per cent in twenty-four surgically treated patients and 45 per cent in twenty-two control subjects. In those who had been free of cerebrovascular complications prior to the operation and in whom adequate postoperative data were available, the incidence of such complications during the follow-up period was 28 per cent in sixty surgical patients and 24 per cent in sixty-eight control subjects. Neither of these differences is statistically significant, but the trend of the results makes it seem highly unlikely that the study of a larger series of cases would indicate that sympathectomy is of major value in preventing the occurrence or recurrence of cerebrovascular accidents. This opinion is strengthened by the fact, already referred to in the section on blood pressure, that two of the patients whose blood pressure had decreased by 2 or more grades following sympathectomy were among those who suffered their first cerebrovascular accident during the postoperative period, the complication being fatal in one (No. 78S), and permanently incapacitating in the other (No. 44S). Moreover, the severity of the strokes which occurred during the ten-year

period seems to have been at least as great in the surgically treated patients as in the control subjects, since they were fatal in sixteen of thirty-two (50 per cent) of the former and in twelve of twenty-six (46 per cent) of the latter, the corresponding mean survival times having been forty-one months and fifty-six months, respectively.

Renal Status. In all three items in the renal panel there was a tendency for the surgically treated patients to fare better than the control subjects. Owing to the fact that all but relatively minor degrees of impairment of renal function are regarded as absolute contraindications to sympathectomy, this investigation provided little or no opportunity to test the ability of the operation to bring about significant improvement in renal function. However, the proportion of surgically treated patients in whom renal symptoms, proteinuria or renal function became significantly worse during the follow-up was only 15 per cent, 5 per cent and 26 per cent, respectively, as compared with 25 per cent, 16 per cent and 36 per cent in the control subjects. None of these differences taken by itself is statistically significant at the 5 per cent level (although this level is almost reached by the figures for proteinuria), but the data for the renal panel as a whole definitely suggest that sympathectomy decreased the rate of progression of the nephrosclerotic process in the kidneys of some of the patients in this series. This opinion is strongly supported by the fact that uremia was the principal cause of death, or an important contributing cause, in twenty-two patients in the control series as compared with only nine in the surgically treated group.

Ophthalmoscopic Findings. It is generally recognized that retinopathy and papilledema are the two manifestations of hypertension which are most likely to subside when the blood pressure is reduced by any form of therapy. Experience with the rice diet [19] and with hypotensive drugs [20] as well as with sympathectomy has shown that even temporary and incomplete control of the blood pressure may be sufficient to cause marked improvement in these complications. The results of the present study, as summarized in Table v, are in full agreement with this view since they show that sympathectomy was significantly more effective than symptomatic management in bringing about the resolution of retinopathy and papilledema, as well as in reducing the frequency with which

TABLE VIII CAUSES OF DEATH IN SURGICAL AND CONTROL SERIES

			M	ales					Fen	nales					To	otal		
Principal Cause of Death		urgic 8 cas			Contr 18 cas	-		Surgic 50 cas			Contr i0 cas			urgic 8 cas		1	Control 8 cas	
The parent of Pean	1	No. of	Patie	ents I	Dead a	at	1	No. of	Patie	ents I	Dead a	at	2	No. of	Patie	ents D	ead a	at
,	2 Yr.	5 Yr.	10 Yr.	2 Yr.	5 Yr.	10 Yr.	2 Yr.	5 Yr.	10 Yr.	2 Yr.	5 Yr.	10 Yr.	2 Yr.	5 Yr.	10 Yr.		5 Yr.	10 Yı
Cerebrovascular accident*	3	6 3	9 5	2 3	5 5	6	1 1	6 2	7 3	1 2	2 3	6 4	4 2	12	16	3 5	7 8	12
Myocardial infarction	1 2	3 2	6 2	0	2 8	4 10	0 2	1 3	3	0 2	1 5	3 7	1 4	4 5	9 5	0 10	3 13	17
Postoperative complications Total deaths	1 8	1 15	23	11	20	26	5	1 13	1 17	5	11	20	13	28	40	18	31	46

^{*} Includes patients listed in Table 11 and 111 as having died of cerebral hemorrhage (CH) and cerebrovascular accident (CVA).

† Includes one patient listed as having died of hypertensive cardiovascular disease (HCVD). ‡ Includes four patients listed as having died of malignant hypertension (MH).

these complications occurred in patients who had been free of them at the start of the follow-up period.

Although the data on abnormalities of the retinal arterioles are somewhat less reliable than those on retinopathy and papilledema because of the use of different systems of grading in the two series, it is of interest to note that improvement of 2 or more grades was observed in nine of thirty surgical patients, but not in a single patient in the control group.

Mortality Rate. Table v shows that the death rate for the series as a whole at the end of ten years was 41 per cent in the surgical patients and 47 per cent in the control subjects, the difference in favor of the surgically treated patients being of the same order of magnitude in males and females. The analysis of death rates at two, five and ten years (Table VIII) shows that the difference between the two series is also fairly consistent throughout the ten-year period.

Sex differences in mortality rate are evident on inspection of the last two columns in Table II and III, and the figures in Table v show that the rate was lower in females than in males, not only in the surgical series (34 per cent as compared with 48 per cent) but also in the control subjects (40 per cent as compared with 54 per cent). Although, in a series of this size, these percentage differences are not statistically significant, the trend of the results is in accord with the conclusions of all studies reported in the literature. Some of the factors which may contribute to the

occurrence of a higher mortality rate in male patients will be discussed subsequently, in the light of the results which are presented in the next paragraph.

The influence of preoperative hypertensive "complications" on mortality rate is clearly demonstrated by the figures given in Table v for the three preoperative "severity" groups into which the surgical and control series have been divided. For example, the ten-year mortality rate in the surgically treated males was 18 per cent in group A (no preoperative complications), 48 per cent in group B (complications other than papilledema) and 80 per cent in group C (papilledema with or without other complications), the corresponding figures for the male control subjects being 14, 58 and 100 per cent, respectively. There were similar differences in mortality rate between groups A and B in the female patients, but the differences between group B and group C were less striking. The relatively low mortality rate of 60 per cent in the female patients with papilledema is probably due to the small number of such cases in this series, together with the fact that only the earliest detectable stage of Keith-Wagener grade 4 retinopathy had been present preoperatively in the two surgically treated patients in group C and the two control subjects who survived the ten-year follow-up period.

The higher death rate in patients with preoperative complications, especially papilledema, and the fact that such complications were more frequent in men than in women, are probably

sufficient to account for a large fraction of the sex difference in over-all mortality rates in the present series. There are, of course, several good reasons for the belief that men are inherently less capable of withstanding the damaging effects of hypertension on the cardiovascular system; for example, the incidence of the more severe degrees of coronary atherosclerosis is known to be higher in middle-aged men than in women of comparable age, even in the absence of hypertension. Nevertheless, the results of this study suggest that the higher male mortality rate, which is so regularly reported in followup studies on hypertensive patients, in part may be due to the fact that men without obvious disability due to the disease are less easily persuaded than women of comparable clinical status to accept any form of treatment, or even to cooperate in a long term program of regular clinical supervision.

The extent to which the height of the blood pressure has influenced the death rate of the patients in this series deserves additional comment, because the use of sympathectomy in the treatment of hypertension is based on the assumption that prognosis will be improved to an extent which is more or less proportional to the reduction in blood pressure which is brought about by the operation. Since the cases in Tables 11 and III are arranged in order of increasing preoperative blood pressure grade, the tendency of the mortality rate to increase with blood pressure is clearly indicated by the concentration of a majority of the entries in the column headed "Cause of Death" in the lower portions of the tables. The occurrence of an appreciable number of death entries in the upper sections of the tables merely emphasizes the fact that the presence of hypertensive complications exerts an unfavorable influence on prognosis, regardless of the height of the blood pressure. For example, of the seventeen patients who failed to survive ten years in spite of having had a relatively low preoperative blood pressure (grade 1 or grade 2 in either systolic or diastolic pressure), there were fifteen (88 per cent) who had shown one or more complications (as defined in the footnote to Table v) during the preoperative period.

Looking at the problem from a slightly different point of view, the fact that entries in the "Cause of Death" column in Tables II and III tend to occur in pairs may be cited as evidence that the matching of surgical patients with control subjects on the basis of over-all preoperative

clinical profile has produced a greater similarity of prognosis in the two series than would have been obtained if the blood pressure level had been the only factor taken into consideration. On the other hand, the occurrence of a significant proportion of ten-year survivals in the patients in the lower half of the tables makes it clear that neither the blood pressure level nor the presence of complications can be relied on to provide a completely satisfactory prognostic index.

Two patients in the control series (Cases 41C and 99C) may be cited as outstanding examples of the limitations inherent in any method of predicting the prognosis of hypertension on the basis of the clinical findings at the start of the period of observation. Case 41C was a fifty-year old man with a maximum preoperative blood pressure of 300/180 mm. Hg, an abnormal electrocardiogram and occasional retinal hemorrhages; he survived ten years, although with slowly progressive cardiac impairment, in spite of the fact that his blood pressure was recorded as high as 300 systolic and 170 diastolic during the postoperative period. Case 99C was a forty-seven-year old woman with a less extreme elevation of blood pressure (highest preoperative reading, 250/150 mm. Hg) who was still alive and free from serious disability at the end of the ten-year interval. In this patient, the disease ran a relatively benign course, in spite of the fact that at the start of the follow-up period she had an abnormal electrocardiogram, proteinuria and occasional retinal hemorrhages, and had suffered a major cerebrovascular accident.

It must be emphasized, however, that such cases are distinctly unusual, and that patients with high blood pressures are more likely to be alive ten years later if their blood pressure is reduced than if it is permitted to continue at the same level. For example, the over-all mortality rate in forty-two surgically treated patients with grade 4 preoperative systolic or diastolic blood pressure was 64 per cent, but in thirteen patients whose pressure was significantly reduced the death rate was only 15 per cent, as compared with 86 per cent in those in whom the blood pressure was not reduced. The overall mortality rate in the control subjects whose preoperative blood pressures were elevated to a similar extent was 72 per cent; this rate is only slightly higher than that of the surgically treated group, but it is of interest to note that both control subjects whose blood pressure

underwent a "spontaneous" reduction of 2 grades were still alive at the end of ten years.

Another observation of interest is the fact that the death rate was only 15 per cent in the control subjects who were paired with the twenty surgically treated patients whose blood pressure was significantly reduced and who were alive and without serious disability at the end of ten years. This suggests that many of the patients whose blood pressure responds favorably to the operation are drawn from a group in which the prognosis without treatment is also relatively good.

Cause of Death. The principal and contributing causes of death listed in Tables II and III are subject to the usual inaccuracies caused by errors in differential diagnosis, especially between cerebral hemorrhage and myocardial infarction, in patients who die suddenly. Other errors have probably arisen as a result of the difficulty of deciding which of several complications should be listed as the principal cause of death in certain patients who died of longstanding, hypertensive cardiovascular disease.

In preparing a summary of the data on the cause of death of the patients in this series (Table VIII), we have accepted the first item listed in the tables as the principal cause of death in each case; therefore, patients shown as having died of heart failure and uremia (HF, U) were placed in the same group as those who died of heart failure alone. One surgically treated patient who was shown on the death certificate as having died of "hypertensive cardiovascular disease" was also arbitrarily assigned to the heart failure group. Under the heading "uremia" we have included not only the patients in whom the cause of death was coded U, or U, HF, but also two surgical patients and two control subjects who were certified as having died of "malignant hypertension." Three of these four patients were known to have had nitrogen retention prior to death, but the terminal renal function of the fourth patient was not known, his assignment to the renal failure group having been made purely on the basis of probability. Our policy with respect to postoperative deaths was to list under this heading any patient who died before discharge from hospital after the operation, even though a direct cause and effect relation could not be established. There were only two such deaths, a female patient who died of bronchopneumonia on the fourth postoperative day, and a man who died as the result of a myocardial infarction on the sixth day.

Table VIII lists for each of the principal causes of death, the number of patients of each sex in the surgical and control series who died before the end of the second, fifth and tenth years of the follow-up period. The deaths are listed in a cumulative manner so that the number shown in the five-year column includes the cases shown in the two-year column, and the ten-year figure represents the total number of deaths.

For each sex separately, and for the series as a whole, the surgical and control groups were remarkably similar with respect to the number of deaths caused by cerebrovascular accidents, heart failure, and myocardial infarction, as well as in the times at which these deaths occurred. The slightly higher death rate from cerebrovascular accidents in the surgical series has been mentioned previously; it is of interest, although not statistically significant. It is also somewhat surprising to note that the cardiac deaths were almost equally divided between heart failure and myocardial infarction, in males as well as in females, and in the surgical series as well as in the control series. Thus the only significant difference between the two series, as far as cause of death is concerned, appears to be the much lower frequency of uremia as the principal cause of death in the surgically treated patients, namely, five of forty deaths, as compared with seventeen of forty-six deaths in the control group $(X^2 = 5.2; P < 0.03).$

Assuming that the cases in the surgical and control series are a reasonably representative sample of the hypertensive population from which candidates for sympathectomy are usually drawn, the data suggest that the slight favorable effect of the operation on mortality rate may be due to its ability to reduce the incidence of death from renal failure by a margin somewhat greater than that required to offset the small operative mortality. In this series the margin of superiority of the operation was also reduced by the occurrence of a slightly higher death rate from cerebrovascular accidents in the surgically treated patients.

These results are consistent with the hypothesis that renal failure, and the "malignant phase" of hypertension which often precedes it, are the complications of the disease which are most directly correlated with the degree of elevation of the blood pressure, and are therefore the ones most likely to be prevented or post-

poned by any form of treatment which produces a significant reduction of the blood pressure. Cerebrovascular accidents and myocardial infarction (and heart failure, insofar as it is due to myocardial ischemia), on the other hand, being due in large part to organic narrowing of the cerebral and coronary arteries, might be expected to show a less favorable response to any type of therapy which reduces the blood pressure without exerting any specific effect on the associated organic vascular disease.

Duration of Survival in Dead Patients. The figures given at the bottom of Table v show that the mean duration of survival of patients who died before the end of the ten-year follow-up period was approximately the same in men and women. Survival time varied markedly, however, from one preoperative "severity" group to another so that there was a more or less reciprocal relationship between mortality rate and duration of survival. For example, if both sexes are taken together, the mean survival times of surgically treated patients in groups A, B and C were seventy-seven, fifty-two and twenty-one months, respectively, while the mortality rates were 13, 48 and 73 per cent. The corresponding figures for the control group were eighty-eight, fifty-two and fourteen months for the survival times, and 16, 54 and 87 per cent for the mortality rates. It was hoped that the figures for duration of survival might reveal a favorable effect of the operation on the course of the disease even in patients who did not survive ten years, but except perhaps in the patients with papilledema (group C), this does not seem to have been the case. The figures for the mean survival time of the dead patients in the surgical and control series as a whole are remarkably similar, namely, forty-six months for the forty surgically treated patients and forty-five months for the forty-six control subjects who died before the end of ten years.

It is recognized that figures for mean survival time, based on data for dead patients only, do not give credit to the operation for the survival beyond ten years of those patients in the surgical series who would almost certainly have died if they had received only symptomatic treatment. When all the patients have been followed to death it will be possible to calculate the true mean survival times, but for the present, as far as mortality rate and survival time are concerned, the results of this investigation may be summarized adequately by recording the slight

favorable effect of the operation on the former, and the absence of a significant effect on the latter in those patients who died in spite of the operation. This is somewhat analogous to the situation which is often encountered in other forms of surgical therapy, cancer surgery for example, where a significant reduction in mortality may be achieved in those patients in whom complete removal of the tumor is possible, while there may be no prolongation of life, or even a reduction in survival time, in those in whom only partial removal can be achieved.

Condition of Survivors at the End of Ten Years. The last line in Table v presents data on the frequency of "incapacitating" disability due to cardiac, cerebral and renal complications of hypertension in the survivors at the end of the ten-year follow-up period. It was hoped that this statistic would provide some indication of the mortality rate which might be expected beyond the ten-year limit of our observations,* and that it might assist in the interpretation of the mortality data. It is obvious, for example, that the significance of a relatively low death rate at ten years would be greatly diminished if it were known that most of the survivors were seriously disabled. Fortunately, this does not appear to have been the case in either the surgical or the control series. If cardiac symptoms, cerebrovascular accident or renal symptoms of grade 4 severity are accepted as incapacitating complications, only two of fiftyeight surgically treated patients and four of fifty-two control subjects were found to be disabled to this extent at the end of ten years. Even when the analysis is extended to include lesser grades of disability, such as those associated with grade 3 abnormalities of cardiac, cerebral and renal function, the incidence of what may be referred to as "serious disability" was found to be only nine of fifty-eight in the survivors of the surgical series, and eight of fiftytwo in the control series. This relatively low incidence of serious disability (approximately 15 per cent in the survivors in each group) is similar to the figure of 20 per cent reported by Griep et al. [15] who used a definition of serious

^{*} It should be emphasized that, throughout this paper, the term "ten-year follow-up" has been used in a literal sense to denote the tenth anniversary of the operation. Many patients are known to have died shortly after the end of the ten-year period, but no cognizance has been taken of this fact in presenting the data in the various tables.

TABLE IX

COMPARISON OF PREOPERATIVE AND POSTOPERATIVE FINDINGS IN SURVIVORS AT END OF TEN YEARS

	Frequency	y of Deterior		e or More G Profile (%)	rades in Var	rious Items
Findings	Male	s	Femal	es	Tota	1
	Surgical (25 cases)	Control (22 cases)	Surgical (33 cases)	Control (30 cases)	Surgical (58 cases)	Control (52 cases)
Systolic blood pressure	12	18	6	20	9	19
Diastolic blood pressure	0	18	3	10	2	14
Cardiac symptoms	40	45	30	43	34	44
Heart size	12	55	12	53	12	54
Electrocardiographic abnormalities	16	45	9	40	12	42
Headache	0	5	0	3	0	4
Cerebrovascular accident	16	18	12	7	14	12
Renal symptoms	4	18	12	40	9	31
Proteinuria	12	23	6	17	9	19
Renal function	28	27	18	37	23	33
Retinal vessels	20	50	21	40	21	44
Retinopathy	4	9	0	10	2	10
Papilledema	0	0	0	0	0	0

disability which seems to have been roughly equivalent to our grade 3.

The figures given in Table IX represent an attempt to compare the clinical status of the survivors in the surgical and control groups in terms of the frequency with which "deterioration," even as little as a single grade, occurred in the various items in the clinical profile. In spite of the fact that individual changes of this order cannot be considered significant according to the convention adopted throughout this paper, it was hoped that any consistent tendency for such small changes to occur in a series of cases might provide a meaningful indication of the probable future course of the disease.

Although the differences between the surgical and control groups are by no means striking, the data presented in Table IX should probably be regarded as additional evidence of a "favorable" effect of sympathectomy on the course of the disease in a significant fraction of the survivors. This, in turn, must be balanced against the "unfavorable" sequelae of the operation, namely, backache, orthostatic weakness and tachycardia, and excessive vasoconstriction in the upper extremities. It is true that such side effects assume a position of relatively minor importance in the perspective of a ten-year

follow-up, but their combined effect in the immediate postoperative period is reflected in the fact that the average time required by the surgically treated patients* to regain their preoperative capacity to carry on their usual occupations was about six months in men and nine months in women. At the end of ten years, however, little or no disability could be attributed to the direct sequelae of the operation, although several patients still complained of abnormal coldness of the hands and a few appeared to have persistent, relatively mild backache.

On the whole, therefore, it would appear that the general clinical condition of the average surgically treated patient who was still alive at the end of ten years was only slightly better than that of the average survivor in the control series. There were, however, a few cases in the surgical series, Case No. 38S, for example, whose over-all clinical condition was definitely better at the end of the follow-up period than it had been before the operation. The significance of such results should not be ignored merely because they are relatively uncommon, since similar

^{*} Excluding those who, at the time of operation, had been unable to work as a result of complications of the disease.

unequivocal improvement was never observed in the control subjects.

SUMMARY AND CONCLUSIONS

1. A ten-year follow-up study has been carried out on one hundred patients (fifty consecutive men and fifty consecutive women) in whom thoracolumbar sympathectomy was performed for the treatment of primary (essen-

tial) hypertension.

2. The clinical course of each patient has been condensed into a series of fourteen four-digit code numbers, one for each of the principal clinical and laboratory findings which reflect the evolution of hypertensive vascular disease in respect to blood pressure, cardiac, cerebral, renal and retinal changes. Each digit in a code number indicates the patient's status with respect to the corresponding item in the clinical profile on a semiquantitative 0 to 4 scale. The first digit of each number refers to the preoperative period, while the second, third and fourth digits describe the situation at the end of two, five and ten years, respectively.

3. Control data were obtained from the records of nearly 1,500 patients who had received symptomatic therapy only, and who had been followed up in one of three cooperating Hypertension Clinics for a minimum of ten years, or until death. The matching of propositi and control subjects was "blind," on the basis of the initial findings only, so that each surgically treated patient was paired with a control subject of the same sex and of closely similar age, and who resembled the propositus as closely as possible with respect to the "preoperative" grades for each of the thirteen items in the

clinical profile.

4. Control subjects who were adequately matched according to our criteria were found for all fifty female patients and for forty-eight of the fifty male patients in the surgical series. The method used in the selection of the control subjects has several admitted shortcomings, most of which are unavoidable in any retrospective study, but detailed comparison of the "preoperative" clinical findings in the two series did not indicate systematic bias in either direction.

5. The coded data for the surgically treated patients and the corresponding control subjects

are presented in full in tabular form.

6. A "significant" reduction in blood pressure was arbitrarily defined as a decrease of 2 or more grades in the average blood pressure

measured under "casual" conditions with the patient in the lying or sitting position. A lasting blood pressure reduction of this degree occurred in about one-third of the patients in the surgical series, but when those who died or suffered major complications in spite of the decrease in blood pressure were excluded, there remained only ten men and ten women whose blood pressure was "significantly" reduced, and who were alive and well at the end of ten years. A similar favorable outcome occurred in only one patient in the control series.

7. The operation was more effective in reducing the average level of blood pressure than in preventing the occurrence of occasional high values which, even in patients with the most clear-cut reduction of blood pressure grade, often reached levels almost as high as the highest recorded preoperatively. The average difference between the maximum preoperative and maximum postoperative blood pressures of the surgically treated patients was a decrease of 21 mm. systolic and 15 mm. diastolic, as compared with an increase of 7 mm. in the systolic pressure and no change in the diastolic in the control subjects.

8. Orthostatic hypotension, which occurred in almost all patients in the immediate postoperative period, was still present in about half of the survivors at the end of two years, the proportion being at least as high in those who were destined to die within the next eight years as in those who survived the full ten-year period. Relatively slight degrees of orthostatic hypotension were still present in about 20 per cent of the survivors

at the end of ten years.

9. Improvement of 2 or more grades in cardiac status did not occur in any patient in the control series, but at the end of ten years cardiac symptoms had improved to this extent in two surgically treated patients, and electrocardiographic abnormalities had decreased by 2 grades in another. The incidence of "unfavorable" changes in cardiac status was lower in the surgical series than in the control series, the frequency of deterioration in cardiac symptoms, heart size and electrocardiogram being 37, 4 and 14 per cent, respectively, in the surgical series, and 43, 19 and 26 per cent in the control subjects.

10. Headache of moderate severity was significantly improved in 58 per cent of the surgically treated patients and in 41 per cent, of the control subjects, but headache of grade 4

FEBRUARY, 1960

220

severity was seldom relieved, all six patients with headache of this intensity having died after an

average interval of only eight months.

11. Cerebrovascular accidents occurred during the ten-year period in 62 per cent of the surgically treated patients who had had a stroke before the operation, and in 28 per cent of those who had not, the corresponding figures for the control series being 45 per cent and 24 per cent, respectively. In several instances post-operative cerebrovascular accidents occurred in patients in whom sympathectomy had produced an apparently significant reduction in blood pressure.

12. Patients with serious renal impairment were not accepted for operation, consequently the results of this investigation do not provide any information on the ability of sympathectomy to bring about improvement in renal function. However, there is reason to believe that the operation may have had a "protective" effect on the kidneys, because the incidence of deterioration in renal symptoms, proteinuria and renal function was only 15, 5 and 26 per cent in the surgically treated patients, as compared with 25, 18 and 36 per cent in the control

subjects.

13. Since the main objective of this project was to evaluate the over-all effectiveness of sympathectomy in a consecutive series of cases, the number of patients with papilledema was relatively small. Nevertheless, the results in the fifteen pairs of cases in this series were in agreement with the consensus of the literature in showing that the operation is highly effective in bringing about the disappearance of papilledema and retinopathy, and in preventing these complications from developing in patients who were free of them initially. Disappearance of papilledema and retinopathy occurred in many patients in whom reduction in blood pressure was only partial and temporary, and also in several who eventually died of various hypertensive complications.

14. The mortality rate at the end of ten years was 41 per cent in the surgical series (48 per cent in males; 34 per cent in females), and 47 per cent in the control series (54 per cent in males; 40 per cent in females). A large fraction of the sex difference in mortality rate was due to the higher incidence of serious preoperative

hypertensive complications.

15. The presence during the "preoperative" period of certain cardiac, cerebral, renal and

retinal abnormalities which have been referred to in the text as "complications" exerted a markedly unfavorable influence on mortality rate, regardless of the height of the blood pressure. Thus in the surgical series the ten-year mortality rate was 13 per cent in patients without preoperative complications (group A), 48 per cent in those with complications other than papilledema (group B) and 73 per cent in those with papilledema (group C), the corresponding rates in the control series being 16, 54 and 87 per cent.

16. Cardiac failure and/or myocardial infarction were responsible for seventeen deaths in each series, but fatal cerebrovascular accidents occurred slightly more often in the surgical series (sixteen cases) than in the control group (twelve cases), while death from renal failure was much less frequent in the former (five cases) than in the latter (seventeen cases). The mortality rate in the immediate postoperative period was 2 per cent.

17. The mean survival time of the dead patients was forty-six months in the surgical series (seventy-seven months in group A, fifty-two months in group B and twenty-one months in group C), the corresponding figures for the control series being forty-five months in the series as a whole and eighty-eight, fifty-two and fourteen months in groups A, B and C,

respectively.

18. The clinical condition of those who survived the ten-year follow-up period was relatively satisfactory, the incidence of serious disability due to complications of the disease having been only 15 per cent in each series. However, in almost all items of the clinical profile, minor degrees of deterioration were distinctly less frequent in the surgically treated patients than in the control subjects. This difference may be reflected in the mortality rate in the next five or ten years.

19. The results of this investigation confirm previous reports that thoracolumbar sympathectomy brings about favorable and occasionally dramatic changes in some of the clinical manifestations of hypertension in certain patients. However, as judged by the results of a direct comparison between surgically treated patients and individually matched control subjects, the over-all effect of the operation on morbidity and mortality in this small consecutive series of cases was somewhat disappointing.

20. The availability of a wide variety of more

or less effective drugs for the treatment of hypertension has greatly reduced the number of patients in whom it is possible to observe the natural course of the disease. We intend, therefore, to use an expanded version of the numerical code described in this paper to summarize a substantial number of the control records which are now available, in the hope that such data may be of value in future studies of the effectiveness of antihypertensive drug therapy.

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Testicular Lesions of Periarteritis Nodosa, with Special Reference to Diagnosis*

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THE ultimate criterion for the diagnosis of periarteritis nodosa is the histopathologic demonstration of typical arterial lesions, and the definitive diagnosis rests largely with the pathologist. Biopsy of muscle, the most common method of obtaining tissue for microscopic examination, provides diagnostic material relatively infrequently and is of no value for the exclusion of that diagnosis. Expressions of the usefulness of biopsy of muscle in the diagnosis [1] of periarteritis nodosa range from skepticism [2] to positive results in 35 per cent of cases [3].

Microscopic examination of excised cutaneous and subcutaneous nodules may supply diagnostic information, but no more than 20 per cent of patients who have periarteritis nodosa present specific cutaneous lesions [4]. In not a few patients, the diagnosis has been made by laparotomy because of unexplained abdominal pain.

The need for aid in establishing the diagnosis of periarteritis nodosa is clear. With few exceptions, published case reports concerning periarteritis nodosa in males either describe lesions in the arteries of the testes at necropsy or else fail to mention the generative organs. For these reasons, and also because approximately three fourths of patients who have periarteritis nodosa are males, a study of the nature and frequency of testicular lesions in this disease was undertaken, especially to determine the suitability of the testis as a site for biopsy.

Testicular lesions in periarteritis nodosa have been recognized for a long time. In 1905, Mönckeberg [5] listed testicular arterial involvement in four of eleven accumulated cases. Jones [6] reported eleven cases of periarteritis nodosa in males in 1942. The genital organs were examined at necropsy in seven of these cases, and lesions were found in all seven. Typical

lesions of periarteritis nodosa in the internal spermatic artery, in the arteries within the substance of the testis, and in the epididymis have been observed at necropsy. Anemic and hemorrhagic infarcts have been described in this disease, as have scarring of the testis and infarction of the epididymis.

Symptoms and signs referable to the gonads in patients who have periarteritis nodosa have included testicular pain, tenderness, swelling, nodularity and numbness. Abnormally small testes have been noted during the course of the disease [7]. In many published cases, the histories did not include testicular symptoms, but involvement of the testicular vessels, with varying degrees of injury to the testicular parenchyma, was demonstrated at necropsy.

In the present study, the diagnosis of periarteritis nodosa was used in the broad sense that has developed over the years to include those disease states in which acute segmental necrosis of small and medium-sized muscular arteries occurs in any or all organs of the body. The study includes lesions that other observers would classify as classic periarteritis nodosa, hypersensitivity or allergic angiitis, and allergic granulomatous angiitis [8]. Subclassification Has merit in attempts to obtain information concerning the cause or causes of this group of diseases. For practical purposes, subclassification of periarteritis nodosa appears to be in advance of existing information. We agree with Ehrich [9] that, at present, it appears best to consider these types as variations of the same disease rather than distinct entities.

Arkin's [10] detailed description of the lesions of periarteritis nodosa is generally accepted, as is his division of their progression into four stages, namely degenerative, acute inflammatory, gran-

^{*} From the Mayo Clinic and Mayo Foundation, Rochester, Minnesota. Abridgment of thesis submitted by Dr. Dahl to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Pathology. Dr. Dahl was on assignment from the U. S. Air Force. The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

ulation tissue and healed. Thrombosis and proliferation of intimal connective tissue produce ischemia and infarction in the tissue supplied by damaged arteries. Formation of aneurysms may lead to arterial rupture and hemorrhage.

MATERIALS AND METHODS

The clinical records, necropsy protocols, formalinfixed gross testicular tissue, and histologic slides of forty-four male patients in whom a diagnosis of periarteritis nodosa had been confirmed or established at necropsy at the Mayo Clinic during the years 1931 to 1955, inclusive, were reviewed.

CLINICAL DATA

The forty-four males with periarteritis nodosa included in this study ranged in age from eleven to seventy-one years, with a mean of forty-six years and seven months. The diagnosis of periarteritis nodosa was established before death in nine of the forty-four patients, and it was considered but not established in twenty-one others. The diagnosis was made by clinical means alone in four patients and with the aid of biopsy in five others. A total of twenty-two specimens of muscle were obtained by biopsy from sixteen patients. In seven of these specimens, representing four patients, diagnostic arterial lesions were found. Biopsy of a subcutaneous lesion established the diagnosis in one patient.

Abnormalities of the scrotal content were apparent clinically in eight of the forty-four patients. Four men complained of sudden onset of "soreness" or pain in one testis from one to four months after onset of their illness. In one of these patients, transient swelling of the opposite testis, which lasted ten days, occurred simultaneously with the testicular pain. A tender epididymis on the side of the painful testis was found in two patients. A decrease in testicular size was described during the illness in four patients; this was unilateral in one instance.

PATHOLOGIC FINDINGS

The testes of forty-one of these forty-four male patients were abnormal. Specific arterial lesions of periarteritis nodosa were present in the gonads of thirty-eight of these patients. (Fig. 1.) Such lesions were apparent within the testicular parenchyma in nineteen patients, involved vessels of the tunica vasculosa in twenty-two, and occurred within the epididymis in twenty-five of thirty-seven patients from whom sections of epididymis were available for examination. Non-specific abnormalities affected the arteries to the testes in three of six patients who did not have gonadal arterial lesions of periarteritis nodosa. These non-specific changes included

leukocytic infiltration, proliferation of intimal connective tissue, thrombosis with or without organization, and replacement of the arterial wall by connective tissue; evidence of previous segmental damage to the artery was absent.

The testes of twelve patients contained recent infarcts. The zones of necrosis ranged in size from 3 mm. in greatest dimension to destruction of the entire testicular parenchyma on one side in one patient. The larger infarcts had an irregular outline and involved many testicular lobules. Smaller infarcts, limited to the confines of one or several lobules, sometimes were situated beneath the tunica albuginea, sometimes swept in triangular or crescentic form from the tunica albuginea to near the mediastinum testis, and in some cases were entirely surrounded by surviving parenchyma. Recent infarcts were all, at least in part, hemorrhagic, although anemic necrosis predominated in some parts. (Fig. 2.) These lesions had the common histologic features of necrosis, most prominently of the tubular epithelium but also of interstitial cells and stroma, dilatation of capillaries and veins at the margins of the lesions, and extravasation of blood within and about the infarcted zone. Even in otherwise completely necrotic regions, outlines of the testicular tubules persisted. Polymorphonuclear leukocytes in large numbers were present within and about the necrotic zones in eight of the twelve recent infarcts.

The presence of necrotic zones with few acute inflammatory cells, but with some macrophages and beginning fibroblastic proliferation, suggested that the infarcts in four patients were slightly older. Grossly, these older lesions were brown or streaked with brown and were more firm than the surrounding parenchyma. In one patient, the entire epididymis on one side, as well as most of the testicular parenchyma on both sides, was infarcted.

Firm white scars, sometimes flecked with yellow or brown, varying from 0.2 to 1 cm. in greatest dimension were found in the testicular parenchyma in thirteen patients. The scars were sufficiently large or numerous in five patients to cause obvious decrease in the size of the involved testis. They were shown histologically to be zones of parenchymal loss, with persistent, thick, hyalinized laminae propriae in dense fibrous connective tissue. (Fig. 3A.) All tubular lining cells had disappeared and, in some lesions, even the tubular outlines had been lost in a homo-

FEBRUARY, 1960

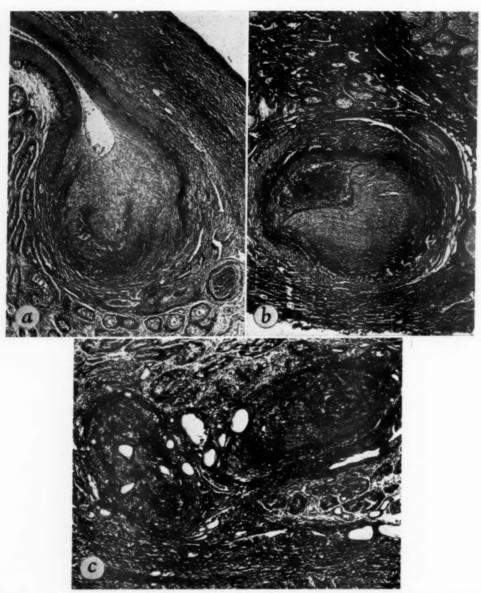


Fig. 1. Testicular lesions in periarteritis nodosa. a, aneurysm in an artery of the tunica vasculosa. Hematoxylin and eosin \times 30. b, acute necrosis with thrombosis in an artery in the tunica vasculosa. Although extensive leukocytic infiltration is present in the wall of the artery, it is not photographically reproduced from the elastic and connective tissue stain used. The entire testicular parenchyma, including the rete testis, is infarcted (\times 35). c, completely healed lesions in arteries of the tunica vasculosa. The eccentric and irregular destruction of the arterial wall, with retention of portions of the elastica interna, is pathognomonic of periarteritis nodosa. Verhoeff elastic tissue stain counterstained with van Gieson connective tissue stain \times 40.

geneous scar. Interstitial cells were present in scattered clusters near the margins of the scars, and it sometimes was difficult to distinguish them from macrophages containing pigment.

Focal loss of tubular epithelium, with thickening, hyalinization and fibrosis of the laminae propriae in scattered small groups of tubules, but with minimal or no stromal alteration, had occurred in the testes of nine patients in addition to the thirteen who exhibited gross scars. Widespread and more or less diffuse

loss of tubular epithelium, with fibrous and hyaline thickening of the laminae, usually accompanied by stromal fibrosis and loss of interstitial cells, had occurred in the testes of eighteen patients. (Fig. 3B.) The testes of eleven of these eighteen patients contained circumscribed healed infarcts as well.

Hematomas more than 1 cm. in diameter had formed in the substance of the testis in two patients. (Fig. 2B.) The ruptured aneurysm responsible for one of the hematomas was demonstrated

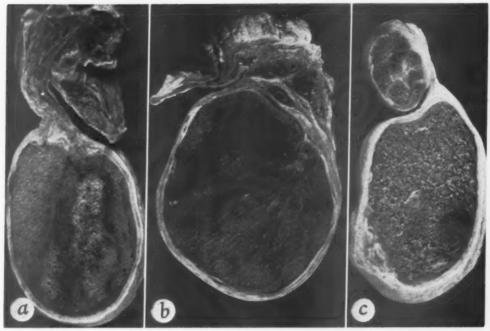


Fig. 2. Testicular lesions of periarteritis nodosa, each enlarged approximately two times. None of these patients had complained of pain in the testes shown. a, large recent infarct. Note the dilated small vessels in the region of the infarct, and the occluded arteries in the tunica vasculosa and epididymis, which is also infarcted. b, hematoma in the right testis. Three weeks before death, the patient had experienced sudden pain in the left testis, which contained small infarcts and hemorrhagic zones at necropsy. c, interstitial extravasation of blood in the testis and epididymis. Note the healed arterial lesions in the parenchyma, tunica vasculosa and epididymis.

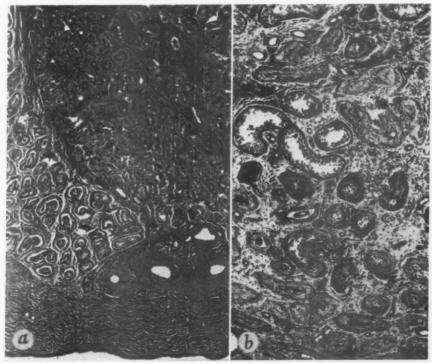


Fig. 3. Ischemic alterations in the testis caused by periarteritis nodosa. a, healed testicular infarct. Hematoxylin and eosin \times 30. b, parenchymal obliteration in the testis of a fifty-six year old man. There is loss of most of the tubular epithelium and the interstitial cells, with fibrosis and hyalinization of both tubules and stroma. Acute and healing lesions of periarteritis (none shown) were present in the arteries to both testes. Hematoxylin and eosin \times 40.

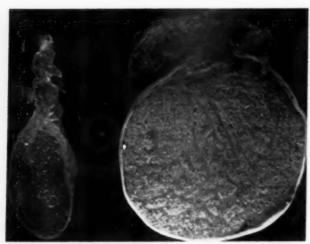


Fig. 4. Cross section of an extremely small testis from a sixty-three year old man with periarteritis nodosa compared with a normal testis (both \times 2). Healed arterial lesions of periarteritis nodosa were present throughout the arteries in the tunica vasculosa, parenchyma and epididymis. The testicular tubules and stroma were largely replaced by hyaline and fibrous connective tissue.

microscopically. Focal interstitial hemorrhage existed in the testes of many (twenty-four of forty-four) patients. (Fig. 2C.)

The testes of eleven patients were abnormally small. (Fig. 4.) In two patients, the decrease in gonadal size was unilateral; in two other patients, it was extremely unequal. This decrease in testicular size had been brought about by incompletely healed infarcts in two patients, by circumscribed scars in five patients, and by diffuse obliteration of the parenchyma in four patients.

The external surface of the tunica vaginalis of many testes exhibited blue or red mottled discolorations where the underlying parenchyma was hemorrhagic or necrotic. The serosal surface remained smooth except in one patient, whose tunica vaginalis on one side was partly obliterated by fibrous adhesions. The affected testis was edematous but contained neither arterial lesions nor ischemic changes in the parenchyma, and the cause of the adhesions was not determined. Except for depressed spermatogenesis and interstitial edema, the testes in three patients were normal. Table 1 summarizes the nature and frequency of lesions found in the testes of the forty-four patients in this study.

In an attempt to assess objectively the frequency of diagnostic arterial lesions in parts of the testis suitable for biopsy, we divided the tunica albuginea and the immediately underly-

Table 1
TESTICULAR LESIONS IN FORTY-FOUR PATIENTS WITH
PERIARTERITIS NODOSA

Lesion	Pat	ients	1	er
Arterial lesions diagnostic of peri-				
arteritis nodosa:	38		86	
Parenchyma		19		43
Tunica vasculosa		22		50
Parenchymal lesions of vascular in-				
sufficiency:	34		77	
Recent infarcts		12		27
Scars (healed infarcts)		13		30
Diffuse parenchymal oblitera-				
tion		18		41
Focal tubular hyalinization		9		20
Hemorrhage:	26		59	
Hematomas		2		5
Interstitial hemorrhage		24		55
Obvious decrease in size of testes	11		25	20

ing parenchyma in one histologic section from each testis into sectors 6 mm. long and 4 mm. deep, and counted the total number of such sectors and the number that contained one or more diagnostic lesions. The dimensions chosen represent removal of a wedge of tissue 6 mm. long and 4 mm. deep, a reasonably sized specimen for testicular biopsy.

A total of 286 such sectors from the testes of these forty-four patients were outlined and examined. Lesions diagnostic of periarteritis nodosa were present in sixty-three sectors, a frequency of 22 per cent.

COMMENT

The 22 per cent frequency of specific arterial lesions in sections of tissue 6 mm. long and 4 mm. deep from the surface of the testis represents our estimate of the chance for the positive diagnosis of periarteritis nodosa by a single random testicular biopsy. Serial or semi-serial sectioning of tissue would be expected to increase the chance of positive diagnosis. Biopsy of a painful or palpably abnormal part of the testis, or of a surgically visible lesion, likewise would be expected to increase the chance of a positive diagnosis.

This figure of 22 per cent is highly vulnerable on statistical grounds, and it may not represent the chance of obtaining a lesion in truly random sampling. Tissue at necropsy is purposely selected to show abnormalities. A similar purpose

guides the surgeon at biopsy, and this figure of 22 per cent has, for our purposes, much more meaning than has the statement that diagnostic arterial lesions were found at necropsy in the testes of 86 per cent of forty-four male patients with periarteritis nodosa. It is apparent that failure to find characteristic lesions of periarteritis in samples of testicular tissue would not help to exclude that diagnosis.

A total of twenty-two biopsies of muscle were performed on the patients in this study during the course of their illness. Seven of the twentytwo samples contained lesions, a frequency of 32 per cent. Because the chance for diagnostic help by testicular biopsy is calculated to be approximately one in five, and because resistance by the patient to gonadal biopsy can be expected, it appears reasonable to recommend testicular biopsy only when, in a patient whose symptoms and clinical findings suggest periarteritis nodosa, the testes are clinically abnormal and there are no cutaneous or subcutaneous nodules available for excision, and no symptoms or signs of lesions in muscles to help in the selection of a site for biopsy of muscle.

Testicular infarction as it occurs after torsion of the spermatic cord usually is severely painful. The visceral layer of the tunica vaginalis has somatic pain receptors, whose stimulation results in pain localized by the patient as "testicular." The parenchyma of the testis has autonomic pain receptors only, and stimulation of these produces a sickening intense pain in the lower part of the abdomen, in the region of the internal abdominal ring [11]. Ischemic testicular lesions, including infarcts, were present in most of our patients; complaints of testicular pain or tenderness were recorded from only four of them. No differences in size or location of the infarcts in patients with and without pain could be demonstrated. One patient with testicular tenderness did not have infarcts; at necropsy, his testes exhibited obliterative parenchymal changes as a result of healed lesions of periarteritis nodosa in the arteries supplying the testes.

That such severe lesions as those in Figure 2A could occur without causing at least some discomfort is surprising. Perhaps so many sources of pain exist in these patients that individual sites are lost in the general aura of suffering and can be demonstrated only by repeated careful examination and specific questioning.

Testicular infarction from causes other than

torsion of the spermatic cord is rare. Winstead [12] collected forty-seven cases of infarction of the testis exclusive of those due to torsion and those occurring in the newborn. In the majority of these patients, the cause for the infarction was not conclusively established, and in none was there a generalized disease that could mimic periarteritis nodosa. Few diseases affecting multiple organ systems are accompanied by testicular symptoms. Mumps and its orchitis, and certain rickettsial infections that produce testicular hemorrhage and necrosis, have a clinical pattern entirely different from that found in periarteritis nodosa. To our knowledge, testicular symptoms have not been described in lupus erythematosus, which may be confused with periarteritis nodosa clinically.

The rarity of the association of clinically evident testicular abnormality and generalized disease suggests that, in the presence of serious disease in multiple organ systems, concomitant symptoms or signs of testicular abnormality should strengthen the clinical suspicion of periarteritis nodosa.

Since specific arterial lesions of periarteritis nodosa were present in the testes of thirty-eight of our forty-four patients, it is not surprising that testicular parenchymal alterations attributable to ischemia were found in thirty-four of the forty-four patients. We have included focal tubular hyalinization among the lesions caused by vascular insufficiency. That ischemia is not necessarily the only or even the primary factor in the genesis of such focal tubular alteration is indicated by the frequent presence of similar lesions in many severe illnesses in which local circulatory disturbances are not postulated [13].

SUMMARY

Significant morbid changes were found at necropsy in the testes of forty-one of forty-four male patients with periarteritis nodosa. Abnormalities included specific lesions in the arteries, recent and healed infarcts, diffuse parenchymal obliteration, focal degeneration of testicular tubules, hematomas and hemorrhage. The testes in a fourth of the patients were obviously smaller than normal. Testicular arterial lesions diagnostic of periarteritis nodosa were found in thirty-eight of the forty-four patients (86 per cent).

Symptomatic or objective abnormalities of the testes were noted clinically in eight of the forty-four patients. The rarity of symptoms and signs

of testicular abnormalities in other generalized diseases suggests that careful search for testicular pain, tenderness or swelling, or a decrease in size of one or both testes in the presence of evidence of vascular disease in other organ systems may aid in establishing the diagnosis clinically.

It is estimated that the diagnosis of periarteritis nodosa can be made by testicular biopsy in one-fifth of male patients who have that disease. Biopsy of a testis may be considered when a clinical testicular abnormality is apparent in a patient suspected of having periarteritis nodosa who does not present any cutaneous, subcutaneous or muscular lesions. Biopsy should include a portion of the tunica vasculosa and of the underlying parenchyma.

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Aldosterone Excretion in Hypopituitarism and After Hypophysectomy in Man*

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Suggestions that secretion of the sodium-retaining hormone of the adrenal cortex was not principally under the control of the adrenocorticotropic hormone (corticotropin) of the anterior pituitary gland had been made previous to the discovery of aldosterone [1]. The evidence was derived in part from histological studies of changes in the adrenal gland following hypophysectomy in animals. In contrast to the atrophy present in the zona fasciculata and zona reticularis, the zona glomerulosa was unchanged or even hypertrophied in the hypophysectomised rat [2], monkey [3] and dog [4], although the latter has been disputed [5]. Hypertrophy of the zona fasciculata and zona reticularis, but not of the zona glomerulosa, had been noted in the monkey following stimulation by corticotropin [3], but not in the dog [6]. Suppression of anterior pituitary function by the administration of cortisone resulted in reduction of the width of the zona reticularis and zona fasciculata, but not of the zona glomerulosa, in the monkey [3] and in the dog [6]. These and other histologic studies led to the conclusion that the zona glomerulosa in animals, with the possible exception of the dog, is independent of pituitary control. In these animals the zona glomerulosa is believed to be responsible for the secretion of aldosterone [7-9].

More direct evidence that the presence of corticotropin is not essential for aldosterone production or release is found in the reports of normal or near normal quantities of aldosterone in the urine of patients with hypopituitarism [10,11] and of the persistence of aldosterone secretion (although possibly at lower levels than in the normal subject) in patients [11] and in animals [12,13] following removal of the hypophysis.

The results of corticotropin administration on the production of aldosterone by the adrenal cortex are by no means clear cut. The perfusion of calf adrenal glands with corticotropin resulted in little change in the sodium-retaining activity of the effluent [14]. On the other hand, the production of aldosterone by incubated rat adrenal glands was stimulated by the addition of corticotropin to the medium [15]. In man, assay of peripheral blood for aldosterone before and two and one-half hours after the administration of corticotropin gel showed no increase in sodium-retaining hormone [16]. No increase in the excretion of sodium-retaining factor after adrenal stimulation by corticotropin was observed by Axelrad, Johnson and Luetscher [17] or by Cope and Garcia Llaurado [18]; on the other hand, a twofold increase in sodium-retaining activity in the urine in man was noted by Liddle, Duncan and Bartter [19] following corticotropin administration. An absence of response to corticotropin was reported by Venning and collaborators [20], but in a later paper this group reported slight increases in excretion of sodium-retaining hormone [11]. Muller, Riondel and Manning [21] noted apparently significant increases in aldosterone excretion in five of eight patients given corticotropin. We [22] also have found that the administration of cortico-

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Table 1
EXCRETION OF ALDOSTERONE IN THE URINE OF
PATIENTS WITH HYPOPITUITARISM

Patient, Age (yr.), Sex	Cause of Hypopituitarism	Sodium Intake (mEq./day)	Aldosterone Excretion (µg./24 hr.)
A. V., 58, F	Idiopathic	116 10	7, 6, 6, 3, 2, 2* 4, 7, 2, 3, 5, 2, 7, 2, 2, 2, 5, 6, 6, 6, 4, 4, 3, 6, 8, 10, 9*
W, S., 69, M	Hypophysectomy	140 10	1
		(third day)	
C. P., 52, M	Chromophobe adenoma	140	0, 0
		10	5, 7
H. T., 50, M	Craniopharyngioma	140	6, 2, 1
M. B., 26, F	Sarcoidosis	80	13†
J. H., 35, F	Hand-Schüller-Christian syndrome	140	3, 3, 1, 5
M. B., 29, F	Sheehan's syndrome	140	5, 2, 4, 4, 6, 9
M. G., 45, M	Hypophysectomy	104	5, 2, 4, 4, 6, 9
A. B., 68, F	Idiopathic	80	2, 2, 6

Note: All patients with the exception of J. H. were maintained on cortisone, 25 to 37.5 mg. a day, and thyroid extract, 60 to 90 mg. a day.

tropin to patients on a normal sodium intake was associated with a small but definite increase of aldosterone excretion. Cessation of corticosterone administration resulted in a fall of aldosterone excretion to levels below those of the control period.

The reports quoted indicate that corticotropin is not entirely without influence upon the level of aldosterone output. The data to be presented in this paper support this view.

Until recently there has been little information on the immediate effect of hypophysectomy on the excretion of aldosterone in man. Luetscher [10], Venning [11] and Hernando [22] and their colleagues report normal or near normal levels for the urinary excretion of aldosterone in patients whose pituitaries had been removed for seven or more days. Garcia Llaurado [24] found that the excretion of material with aldosterone-like activity, estimated by bioassay, was unchanged, or only slightly increased immediately following hypophysectomy, whereas in other surgical procedures he had found substantial increases in the excretion of this material [25].

Observations are presented here on the excretion of aldosterone in the urine of four patients, all women, subjected to hypophysectomy for the palliation of carcinoma of the breast. In contrast with the findings of Garcia Llaurado [24], all these patients showed a considerable

increase of aldosterone excretion during the immediate postoperative period.

CHEMICAL METHODS

Aldosterone was measured by the physicochemical method of Neher and Wettstein [26] as modified by Hernando and co-workers [22]. Sodium and potassium concentrations in urine were measured by flame photometry.

CLINICAL STUDIES

Excretion of Aldosterone in Patients with Panhypopituitarism. Aldosterone was measured on twenty-nine occasions in the urine of nine patients suffering from hypopituitarism while receiving a normal intake of sodium, and on seventeen occasions in the urine of three such patients when on a low salt diet. At the time of study all these patients were receiving maintenance doses of cortisone and a thyroid preparation. The causes of their pituitary insufficiency are detailed in Table 1.

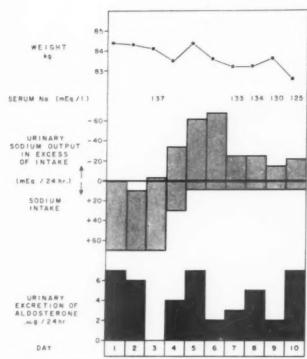
The results of these studies are shown in Table 1. The mean daily excretion of aldosterone in patients on a normal intake of sodium was 2.9 μ g. (S.D. \pm 0.4). The mean for the aldosterone excretion of a series (seventy-two determinations) of normal subjects estimated by the same method was $5.0 \pm 3.0 \mu$ g./twenty-four hours [22]. The difference between means is significant (p < 0.01).

One patient excreted no measurable aldosterone in the urine on control days, but showed measurable amounts when corticotropin was administered. Aldosterone excretion reverted to nil when corticotropin therapy was discontinued.

Day	Therapy	Aldosterone Excretion (µg./24 hours)
1	No corticotropin	0
2	No corticotropin	0
3	Corticotropin, 25 units adminis- tered intravenously over 8 hours Corticotropin, 25 units adminis-	6
4	tered intravenously over 8 hours	3
5	No corticotropin	0

Response of Patient with Panhypopituitarism to Dietary Restriction of Sodium. Normal subjects, when placed on a restricted sodium intake, respond by a reduction in urinary excretion of

[†] This patient also had diabetes insipidus and was not being treated with vasopressin when this urine specimen was collected.



Maintained on Cortisone, 12.5 mg daily, throughout period of study

Fig. 1. Effect of a restricted sodium intake in a patient with hypopituitarism.

sodium and an increase, of varying magnitude, in the urinary excretion of aldosterone [27]. Patients with panhypopituitarism are capable of adapting slowly to a restriction of sodium intake. They do not usually go into circulatory collapse as do patients with Addison's disease subjected to the same stress. This difference in response may be the consequence of the persistence of aldosterone secretion in patients with hypopituitarism, as opposed to patients with Addison's disease. Therefore, a patient with panhypopituitarism has been studied to determine the response of aldosterone excretion (and so presumably of aldosterone secretion) to dietary restriction of sodium.

The results of this study are shown in Figures 1 and 2. On the first occasion, patient A. V. did not achieve sodium balance but symptoms developed (weakness, nausea, anorexia, and muscular cramps associated with hyponatremia) which necessitated termination of the study. (Fig. 1.) One month later the study on this patient was repeated and on this occasion sodium balance (by which is meant in this context that the sodium excretion in the urine was less than the sodium intake) was achieved on the twelfth day. (Fig. 2.) It will be noted that the highest level of aldosterone excretion at-

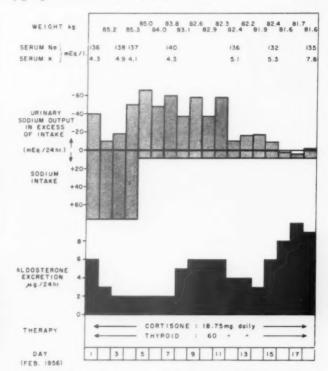


Fig. 2. Effect of a restricted sodium intake in a patient with hypopituitarism.

tained during this period of low sodium intake was 10 μ g. on the thirteenth day of the study. The mean level of aldosterone excretion on the control days was 3.5 μ g./twenty-four hours, and 4.9 μ g./twenty-four hours when on a sodium intake of 9 mEq. daily.

Aldosterone Excretion Following Hypophysectomy in Man. Aldosterone excretion was measured in the urine of four patients before and immediately after hypophysectomy. The patients were on a free but measured fluid intake. The sodium and potassium content of their diets was calculated from the tables of Bowes and Church

These patients were on the Surgical Service of the Peter Bent Brigham Hospital under the care of Drs. F. D. Moore and A. G. Jessiman. Hypophysectomy was performed by Dr. D. D. Matson through a transfrontal craniotomy.

CASE I. H. J. (PBBH No. 3K 879), a thirty-eight year old woman, had a radical mastectomy performed in March 1953 for carcinoma; subsequently multiple metastases developed. Bilateral oophorectomy was performed on December 29, 1956 and hypophysectomy four days later. (Fig. 3.) Cortisone was given, commencing with 150 mg. on the day before and 350 mg. on the day of operation, thereafter being gradually reduced. Diabetes insipidus developed within a few hours of operation, but vasopressin

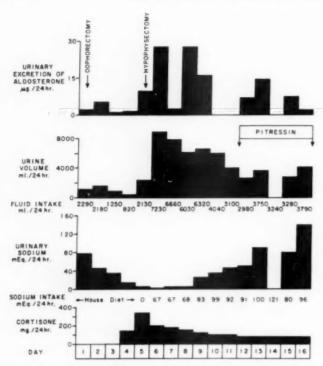


Fig. 3. Case 1. Urinary excretion of aldosterone and of sodium after oophorectomy and hypophysectomy.

(Pitressin®) was not given until a week later. The urinary aldosterone excretion was 2 μ g./twenty-four hours on the day of oophorectomy and remained between 1 and 5 μ g. on the following three days. On the day of hypophysectomy it was 7 μ g. and on the day following 28 μ g. By the eleventh day after hypophysectomy aldosterone excretion had returned to 2 μ g.

Four months after hypophysectomy the patient was readmitted for further study. Her general condition was satisfactory, but she still had diabetes insipidus which was controlled by the use of posterior pituitary (Pitressin) snuff. She was then receiving 50 mg. cortisone daily. After three control days, during which her urine volumes were 2 to 3 L. a day, vasopressin therapy was withdrawn. (Fig. 4.) On the following day the urine volume was 6,520 ml., falling gradually to 4,640 three days later. Urinary aldosterone excretion remained between 3 and 7 μ g. daily during the control days and the first two days after withdrawal of vasopressin. On the third day after vasopressin withdrawal aldosterone excretion rose to 22 μ g., falling to 20, 17 and 4 μ g. on successive days. Up to this time she had been receiving 140 mEq. sodium daily, except for one day when it was 114 mEq.

The sodium intake was then reduced to 13 mEq. daily. As the results of the aldosterone determinations were not available until after this study was completed it was not known at the time that the aldosterone output was still raised on the day before sodium intake was reduced. Aldosterone excretion fell to normal on the first day of the low sodium diet but

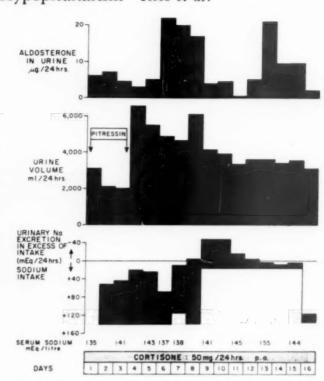


Fig. 4. Case 1. Effect of withdrawal of vasopressin and of a low salt diet on a hypophysectomised patient.

rose on the fifth day to 24 μ g./twenty-four hours. It fell thereafter to 9.5, 9.5 and 2 μ g. on successive days. At autopsy four months later, hypophysectomy was found to have been complete.

CASE II. D. de H. (PBBH No. 3K 964), a thirtyeight year old woman, five and one-half months pregnant, had first noticed a lump in her breast seven months before admission. Biopsy of the breast and of a lymph node in the axilla at another hospital had revealed an adenocarcinoma. It was decided to submit the patient to hypophysectomy in order to prevent the exacerbation of carcinoma of the breast which might occur following delivery. Hypophysectomy was therefore performed on January 7, 1957. Cortisone acetate, 200 mg./day, was administered over the operative period. (Fig. 5.) Diabetes insipidus developed but vasopressin was not given until the sixth postoperative day. Before operation her urine contained 25, 3 and 15 µg. of aldosterone on three consecutive days. Increased aldosterone excretion during pregnancy had also been reported by Venning and co-workers [29], Martin and Mills [30] and Koczorek and co-workers [31]. Urine was not available for aldosterone estimation on the day of and day after operation, but on the following nine consecutive days it contained 21, 34, 18, 106, 12.5, 17, 9, 4 and 36 μ g. of aldosterone. This case has been reported in detail elsewhere [32].

CASE IV. J. de M. (PBBH No. 6J 152), a fifty-three year old woman, had a radical mastectomy for

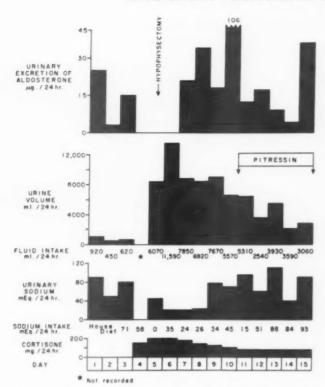


Fig. 5. Case II. Urinary excretion of aldosterone and of sodium after hypophysectomy.

carcinoma in 1948. In January 1956 bilateral oophorectomy was performed because of skeletal metastases, and as the condition was still progressing in April 1956 she was treated with 75 mg. cortisone a day. This was continued until April 1957; during this time the lesions at first improved, but then progressed. Hypophysectomy was therefore performed on April 15, 1957. During the week before operation she was given 400 mg. of cortisone daily; this dose was gradually reduced following hypophysectomy. Diabetes insipidus developed for a few days only, and no vasopressin was given. The urinary aldosterone excretion on the three days before operation was 5, 1 and 3.5 μ g. (Fig. 6.) On the day of operation 1 μ g. of aldosterone was present in the urine, rising to 23 μ g. on the day following, after which it fell over the next three days to 13, 6 and 3 μ g./24 hours.

Case IV. H. F. (PBBH No. 9K 791), a fifty-one year old woman, had a radical mastectomy for carcinoma in 1954. In October 1956 she was found to have skeletal metastases and was treated with 30 mg. testosterone, and 3 mg. prednisone daily. As the disease was not controlled, hypophysectomy was performed on May 6, 1957. On the following day a craniotomy had to be performed in order to evacuate a hematoma which had accumulated in the frontal lobe. No vasopressin was given as the urine volume never rose above 3,500 ml./24 hours. The urinary excretion of aldosterone was 8.5, 1 and 6 μ g. on three days before operation. (Fig. 7.) On the day of

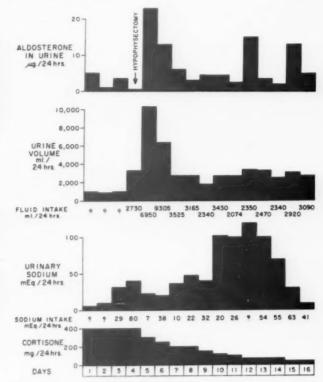


Fig. 6. Case III. Urinary excretion of aldosterone and of sodium after hypophysectomy.

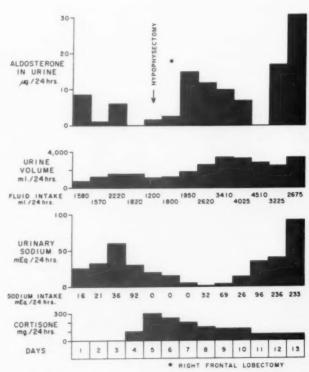


Fig. 7. Case IV. Urinary excretion of aldosterone and of sodium after hypophysectomy.

TABLE II
ALDOSTERONE EXCRETION IN A PATIENT WITH HYPOPITUITARISM WHILE UNDERGOING MAJOR

	PITUITARISM	WHILE	UNDERGOING	MAJOR
	SURG	ICAL PI	ROCEDURES	
-				

Event	Aldosterone Excretio (µg./24 hr.)							
Preoperative days 3	2							
	1.5							
2	5.5							
Excision of carcinoma								
of sigmoid colon	3.5							
Postoperative days 1	9							
2	7.5							
3	****							
4	11							
5	3							
6								
7	4.5							
8	7							
9	4							
10	1							
11	3.5							
12	12.0							
Resuture of abdominal wound								
Postoperative days 1	2							
2	0.5							
3	2.5							
4	2							
5	3.5							
6	1							
7	5.5							
8	0.5							

hypophysectomy aldosterone excretion was 1.5 μ g., and on the following day when the craniotomy was performed, 2.5 μ g. During the next four successive days it was 15, 12, 10 and 7 μ g./24 hours.

Aldosterone Excretion in Patient with Hypopituitarism Following Major Surgical Procedures. The urinary excretion of aldosterone in a patient with hypopituitarism who underwent major surgery for resection of a carcinoma of the sigmoid colon and who, two weeks later, underwent a further operation for repair of dehiscence of the abdominal wound, is shown in Table II. The mean aldosterone excretion during three control days preoperatively was 3 μ g./24 hours. On the day of operation, during which there was massive bleeding, the aldosterone excretion was 3.5 μ g. The mean excretion during the following twelve days was 6.2 μ g. The mean excretion for

the eight days following the second operation was only 2 μ g.

COMMENTS

The results of these studies agree with the results of others in indicating that the pituitary gland is not a major factor regulating the secretion of aldosterone in man. Nevertheless the administration of corticotropin is not entirely devoid of effect on the excretion of aldosterone: under certain circumstances it is capable of causing considerable elevation of aldosterone in normal subjects, as shown, for example, by the response of the same subject on a normal, and subsequently on a low sodium intake, as already reported [23]. Similar responses have been noted by Liddle, Duncan and Bartter [19] and by Muller, Riondel and Manning [21]. Again, we have observed that the prolonged administration of corticotropin gel to a normal subject on a constant sodium intake for a period of twenty-seven days doubled the mean excretion of aldosterone when compared with the preceding control period of equal length [22].

On a normal diet, the mean daily excretion of aldosterone in the nine patients with hypopituitarism was significantly lower than that of normal subjects. There was also much less random variation in the daily levels of excretion in the patient with hypopituitarism. The diurnal variation of aldosterone excretion in these patients was unfortunately not studied, but has been found absent by Muller and colleagues [33].

The response of aldosterone production to restriction of sodium intake was greatly diminished in the patient with hypopituitarism studied here, compared with that of normal subjects [34]. Nevertheless, her sodium excretion, when on a maintenance dose of cortisone, ultimately fell to a figure below that of her intake. It has been observed in normal subjects that when sodium intake is restricted the reduction of sodium excretion is not entirely dependent upon the level of aldosterone [34]. On the other hand, patients with Addison's disease, who secrete no aldosterone, are unable to attain sodium balance under similar circumstances. The presence of aldosterone may thus be a permissive factor in the reaction of the body to this dietary stress.

The data obtained from Cases I to IV demonstrate that not only is aldosterone found in the urine immediately after hypophysectomy in man, but also that it may be present in increased amounts. Increased excretion of aldosterone fol-

Table III

ALDOSTERONE EXCRETION AND URINARY SODIUM/POTASSIUM RATIOS IN FOUR PATIENTS BEFORE

AND AFTER HYPOPHYSECTOMY

Case and Procedure		Days before Operation					Days after Operation													
		4	3	2	1	Operation	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Case I Oophorectomy	Na intake* Urine Na/K Urinary aldosterone†	- * *				House 1.1 2	1.6									1				
Case 1 Hypophysectomy	Na intake* Urinary Na/K Urinary aldosterone†		Hous	e diet	.43	0 .19 10	67	.04	.05		.42	92 .74	.62	1.4		80 1.2 7.5	1.5			8 X X
Case 11 Hypophysectomy	Na intake* Urine Na/K Urinary aldosterone†	Hous 1 7 25	e diet 1.1 3	71 1.7 15	58	0 .63	35	.37	.43	1.1	.9	15 1.1 12.5	1.3	1.4	84					
Case III Hypophysectomy	Na intake* Urinary Na/K Urinary aldosterone†	House diet .07 .14 5 1			29 .39 3.5	80 .43	.29	.22	.42		.91		26 1.5 2.5			.75	63	41 .1 5		
Case IV Hypophysectomy	Na intake* Urine Na/K Urinary aldosterone†	16 .3 8.5	21 .43 1	36 .76 6	92	0 .31 1.5	0 .19 2.5	.1	.05	.06	26 .33 7	.57		1.3			142		.9	diet .92 10

^{*} mEq./twenty-four hours. † µg./twenty-four hours.

lowing surgical operations has been reported by Garcia Llaurado [25] and Zimmerman et al. [35]. Venning and her associates [36] have reported a rise in aldosterone excretion on the day of operation, which fell to within normal limits for several days postoperatively, and then began to increase again. In the present series, one patient (Case 1) had a bilateral oophorectomy four days before removal of her pituitary gland. Although her aldosterone excretion was not measured before oophorectomy it remained within normal limits on the day of, and for three days after this operation, and did not show the postoperative increase noted by Garcia Llaurado [25] and Venning [36] (who used biological methods of assay).

Following hypophysectomy the maximum increase in aldosterone excretion was on the first or second day after operation in Cases I, III and IV, and on the fifth day in Case II. The trend in all cases was a decrease from a high level on the first few days after operation to normal levels a week or so after operation, a pattern which differs from that found by Venning et al. [36] after other surgical procedures.

Normal subjects on a restricted sodium intake excrete increased amounts of aldosterone [10,15,

19,22,27,37]. Sodium intake in the four patients was lowest in the period during and immediately after hypophysectomy. It is not possible to assess the importance of this factor, but the patient who had no intake of sodium on the day of operation, and for two days afterwards (Case IV, Fig. 7), had the smallest increase in aldosterone excretion. Conversely, the patient who had a daily sodium intake of 67 mEq. or more after hypophysectomy (Case I) showed the greatest increase in aldosterone excretion, with the exception of Case II, in which higher figures may be in part attributed to pregnancy.

Garcia Llaurado [24] found slight or no increase in aldosterone excretion after hypophysectomy in man, and correlated this with the slight fall in urinary Na/K ratio after hypophysectomy, compared with that following other surgical operations. In the present series, three patients (Cases I, II and IV) had a well marked fall in urinary Na/K ratio after hypophysectomy at a time when aldosterone excretion was increased. This is shown in Table III. One patient (Case III) had low Na/K ratios in the urine before as well as after operation, and it may be significant that she was receiving 400 mg. of cortisone daily during this period when she had

normal levels of aldosterone in the urine. In all patients, the lowest Na/K ratios in the urine coincided with the period when they were receiving the highest doses of cortisone and we believe that this factor should not be ignored when correlating the increase in urinary aldosterone with urinary Na/K ratio.

It has been shown in man [19,22] that the administration of cortisone in daily doses of 100 to 200 mg. over a period of days did not significantly change the level of aldosterone excretion. Farrell et al. [6] administered 100 mg. of cortisone a day for five weeks to dogs, and found that the rate of aldosterone secretion in the adrenal vein was not reduced. In Case III of the present series the patient received 75 mg. of cortisone a day for a year, and 400 mg. a day for a week before operation. The finding that she not only excreted normal amounts of aldosterone when receiving this dose of cortisone, but also excreted considerably increased amounts following hypophysectomy is further evidence that cortisone given even over a long period did not inhibit aldosterone excretion.

If vasopressin is suddenly withdrawn from patients with established diabetes insipidus the urinary excretion of aldosterone increases, probably as a consequence of the decrease of extracellular fluid volume [37]. Thus following hypophysectomy diabetes insipidus developed in all our patients. Diabetes insipidus was most marked in the two patients (Cases I and II) who had the largest increase in aldosterone excretion following operation. In the other two patients in whom diabetes insipidus was mild (Cases III and IV) there were smaller increases in urinary aldosterone excretion. Unfortunately it was not possible to give vasopressin to any patient throughout the postoperative period in order to eliminate diabetes insipidus entirely, but the authors venture to suggest that aldosterone excretion would not show the same postoperative increase under these circumstances.

One patient (Case 1) was studied again four months after hypophysectomy, when she still had diabetes insipidus which necessitated treatment with vasopressin. On withdrawal of the anti-diuretic hormone her daily urine volume rose from 2 to 6.5 L., and there was a striking rise in aldosterone excretion. (Fig. 4.) Since she was on a constant intake of sodium and her usual dose of cortisone, it seems likely that the rise in aldosterone excretion was the consequence of volume changes following the withdrawal of

vasopressin. The delay of two days after vasopressin withdrawal before aldosterone excretion increased is longer than that observed when diabetes insipidus developed after hypophysectomy in this patient. Seven days after withdrawal of vasopressin her sodium intake was reduced from 140 to 13 mEq. a day. As a consequence aldosterone excretion rose to 21 µg./twenty-four hours on the fifth day of salt restriction. It is significant that four months after removal of the pituitary the stimuli of vasopressin withdrawal and a low sodium intake were both capable of provoking an increase in aldosterone excretion. Such a response is not found in patients who have had hypopituitarism for some years, as shown by patient A. V., but a similar response has been reported by Maclean et al. [39] within a year of hypophysectomy; the actual time following operation is not stated in their paper. However, in a patient known to have had hypopituitarism for seven years, the stimulus of a major abdominal operation involving considerable blood loss doubled aldosterone excretion. (Table II.)

CONCLUSIONS

From these observations it is concluded that aldosterone excretion is significantly below normal in patients with longstanding hypopituitarism when on an unrestricted sodium intake and that the response to sodium restriction or surgical stress also is reduced. However, immediately following removal of the pituitary gland in such patients aldosterone secretion is considerably increased in association with, and probably the consequence of, volume changes due to diabetes insipidus. Moreover, in one of these patients studied four months after hypophysectomy withdrawal of pitressin therapy resulted in almost as great an increase in aldosterone excretion as immediately following operation. It is evident that the capacity of the adrenal cortex to respond to suitable stimuli by an increased aldosterone secretion falls off slowly following loss of anterior pituitary function. These facts suggest that corticotropin, perhaps by maintaining the size of the gland, exerts a tropic effect on the adrenal cortex so that it is capable of an increased rate of synthesis or release of aldosterone in response to the appropriate physiological stimulus.

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Hyperventilation and Arterial Hypoxemia in Cirrhosis of the Liver*

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Patients with cirrhosis of the liver may have a low plasma carbon dioxide content secondary to chronic hyperventilation [1]. The mechanism maintaining the hyperventilation is unknown; since it occurs despite low carbon dioxide tension (pCO₂) and normal, or slightly elevated pH, hypoxemia remains as a potential stimulus for the respiratory center [2]. However, even though oxygen unsaturation of arterial blood and low arterial blood oxygen tensions have been observed in patients with cirrhosis of the liver [3-6], they have been of a magnitude generally assumed to be inadequate for stimulation of a normal respiratory center [7]. A search has been made for alternate, perhaps nonphysiological stimuli, to explain the hyperventilation in patients with cirrhosis of the liver. Roberts, Thompson, Poppel and Vanamee [1,8] have ascribed such a stimulatory effect to the abnormally high concentrations of ammonia in arterial blood [9]. However, correlation is poor between the minute ventilation and the concentration of ammonia in blood, both in patients with cirrhosis of the liver and in animals infused with ammonium acetate [8]. It is, therefore, conceivable that other unknown stimuli are responsible for the hyperventilation. Such stimuli may bypass the liver and arrive at the respiratory center by way of abnormal vascular communications between the portal vein and either the inferior vena cava or the pulmonary veins [10]. The present study was undertaken to establish the coincidence of hyperventilation and hypoxemia in cirrhosis of the liver. The results show that hyperventilation, compensated respiratory alkalosis and low arterial oxygen tension do occur concurrently in patients with cirrhosis of the liver. The low oxygen tension

seems to be best explained by increased venous admixture, conceivably via vascular communications bypassing the alveolar-capillary bed. The mechanism maintaining hyperventilation remains obscure.

METHODS AND MATERIALS

Subjects. Ten patients with cirrhosis of the liver and one patient with schistosomiasis were studied. The patient with schistosomiasis had extrahepatic obstruction of the portal vein, marked esophageal varices and involvement of the liver, all documented during subsequent laparotomy for a portal-caval shunt procedure. The clinical data obtained at the time of study are summarized in Table I.

Plan of Study. The following measurements were made in the fasting subject: (1) Lung volumes and maximal breathing capacity to exclude intrinsic disease of the lung. (2) Resting minute ventilation and oxygen consumption to document hyperventilation in the absence of increased oxygen consumption. In order to minimize the effects of anxiety, minute ventilation was determined after the patient had become familiar with the procedure on preceding days and actual measurements were made only if ventilation had remained constant for fifteen to twenty minutes. (3) Oxygen content, oxygen capacity, and the partial pressure for oxygen of arterial blood, to establish the presence of arterial hypoxemia, i.e., low partial pressure for oxygen. (4) Carbon dioxide content, pCO2 and pH of arterial blood to document the compensated respiratory alkalosis. (5) Diffusing capacity for oxygen, to exclude impaired diffusion as a cause for the low pO2. (6) Arterial blood ammonia ("volatile base") content for correlation with the resting minute ventilation. (7) In vitro equilibration of blood with gas mixtures of known oxygen tension to exclude a shift in the oxygen dissociation curve as a cause for arterial blood unsaturation.

Analytical Methods. The carbon dioxide and oxygen content as well as the oxygen capacity of arterial

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TABLE I

CLINICAL AND LABORATORY DATA ON ELEVEN PATIENTS WITH CIRRHOSIS OF THE LIVER

Patient No., Age (yr.) and Sex	Pilirubin (mg. %)	Cephalin Flocculation	Total Protein* (gm. %)	Bromsulphalein (45 minutes) (%)	Alkaline Phosphatase† (units)	Hemoglobin (gm. %)	Liver Biopsy	Spiders	Varices	Ascites
1, 55, F	0.6	3+	5.9	62	5.6	11.0	+	+	+	++
2, 52, F	11.0	4+	8.2		3.9	8.0	+1	+	+	+
3, 72, M	1.3	2+	7.4	30	7.2	13.6	+	+	-	++++
4, 56, M	0.2	4+	7.6	3	N	11.5		-	*****	per
5, 71, F	1.2	2+	7.0	17	N	10.0	+ 1	-	+	-
6, 56, F	1.7	4+	7.8		N	15.2		+	+	±
7, 57, M	0.6	2+	8.3	7	N	16.2		+	-	-
8, 47, F	2.5	2+	7.3	26	7.3	9.6		+	-	_
9 \$, 50, F	2.1	4+	8.7		N	11.9		+	-	-
10 , 42, M	1.0	3+	7.2	11	7.3	12.2	+	-	+++	+
11, 29, M	13.0	3+	5.7	61	3.9	8.4	+ 1	+	-	++

* All patients had a reduced A/G ratio

† Normal alkaline phosphatase activity indicated by N (upper limit of normal 3 Bodansky units). ‡ Cirrhosis of the liver documented at autopsy.

Patient with postnecrotic cirrhosis

Patient with portal obstruction and disease of the liver secondary to schistosomiasis. This was the only patient with clubbing.

blood were determined by the method of Van Slyke and Neill [11]. Five ml. of blood were equilibrated with room air for ten minutes to establish the oxygen capacity. The partial pressure for oxygen and carbon dioxide in arterial blood were measured by the method of Riley, Proemmel and Franke [12]. The blood ammonia content was determined by the method of Seligson and Hirahara [13]. The blood pH was measured anaerobically at 37°c. with a McInnes-Belcher glass electrode and a Cambridge pH meter. The carbon dioxide and oxygen content of expired

air was determined with a Scholander gas analysis apparatus [14]. The diffusing capacity for oxygen was measured by the method of Lilienthal, Riley, Proemmel and Franke [15].

RESULTS

The results are summarized in Tables II to IV and Figures 1 to 4.

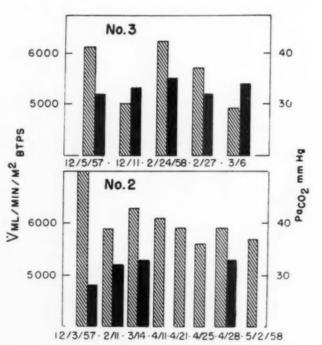


Fig. 1. Minute ventilation (V ml./minute/M2BTPS) and the partial pressure for carbon dioxide (Paco2) in patients 2 and 3 followed over a period of several months. Paco, indicated by solid bars.

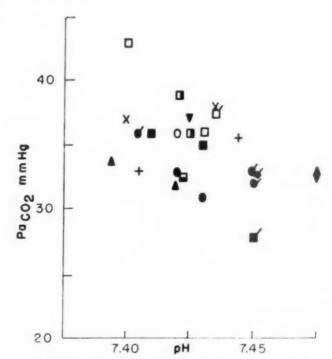


Fig. 2. The partial pressure of carbon dioxide (Paco2) plotted against the pH of arterial blood. Each symbol represents one patient. Most patients were studied more than once. Symbols with a "flag" indicate calculated values for Paco2; all others represent direct determinations.

TABLE II

LUNG VOLUMES, MAXIMAL BREATHING CAPACITY, INDEX OF INTRAPULMONARY MIXING, MINUTE VENTILATION, OXYGEN CONSUMPTION, RESPIRATORY EXCHANGE RATIO AND DIFFUSING CAPACITY IN ELEVEN PATIENTS WITH CIRRHOSIS OF THE LIVER

Patient No.	Body Surface Area (M²)	Vital Capacity (% of predicted)	Total Lung Capacity (% of predicted)	RV/TLC × 100 (%)	7' N ₂ (%)	Maximal Breathing Capacity (% of predicted)	$V_D/V_T \times 100$ (%)	VBTPS (ml./min./M²)	$\dot{\mathbf{V}}_{\mathbf{A}} \; (\mathrm{ml./min./M^2})$	Vo ₂ (ml./min./M²)	V _{CO2} (ml./min./M²)	Respiratory Exchange Ratio	Hd	Pco2 (mm. Hg)	PA ₀₃ (mm. Hg)	A-a (mm. Hg)	Do2 (ml./min./mm. Hg)	Oxygen Saturation (%)
1	1.59	90	97	31	1.8	76	29	5600	3996	156	128	.82	7.40	34	107	28	11.2	94
2	1.60	85	74	37	2.4	106	37	5890	3677	131	114	.87	7.43	35	111	40	20.1	94
				* *		***	34	6340	4196	176	128	.73	7.41	36	101	27		91
3	1.63	91	80	26	2.3	109	35	5470	3538	126	98	.78	7.43	32	114	45	16.9	91
		***		* *		***	33	4780	3235	114	92	.81	7.42	33	115	33	13.8	92
4	1.72	107	106	35	2.6	97	34	4200	2730	114	110	.97	7.40	43	109	15	12.4	93
5	1.65	90	115	49	1.3	121	35	4370	3160	116	90	.78	7.42	36	103	32	13.0	94
6	1.53	98	101	41	2.2	110	30	5420	3788	135	121	.90	7.44	35	114	38	12.1	92
7	1.74	84	80	33	2.7	118	27	4040	3000	154	123	.80	7.40	37	111	36	23.8	95
8	1.40	95	94	29	1.2	122	33	6220	4223	204	139	.68	7.42	39	102	17		99
9	1.79	97	90	35	1.7	83	29	6470	4590	165	152	.92	7.48	33	119	36		90
10	1.53	86	74	25	1.1	138	35	6363	4110	146	129	.88	7.43	37	114	14		100
11	1.90	86	83	19	1.8	82	25	4600	3660	159	117	.74	7.42	32	113	25	16.8	94

Note: RV/TLC = Residual volume to total capacity ratio.

 $7' N_2 = Index of intrapulmonary mixing.$

 $V_{\mathrm{D}}/V_{\mathrm{T}}$ = Physiological deadspace to tidal volume ratio.

 \dot{V}_{BTPS} = Minute volume, body temperature and pressure saturated with water vapor.

 \dot{V}_A = Alveolar ventilation. \dot{V}_{O_2} = Oxygen consumption.

 V_{CO_2} = Carbon dioxide output.

 P_{CO_2} = Carbon dioxide tension in arterial blood.

 $P_{A_{O_2}}$ = Oxygen tension of alveolar air.

A-a = Gradient for oxygen tension between alveolar air and arterial blood.

 D_{O_3} = Diffusing capacity for oxygen.

Lung Volumes and Maximal Breathing Capacity (Table II). The vital capacity (VC) and total lung capacity (TLC) was slightly less than predicted in all subjects. This was associated with a normal residual volume to total lung capacity ratio (RV/TLC) except for patient 5, the oldest subject (seventy-one years of age) and patient 6. The maximal breathing capacity was reduced in the most severely ill patient (1) and an obese woman (9). The index of intrapulmonary mixing (seven-minute nitrogen) was slightly elevated in two subjects (patients 4 and 7). The ratio of physiological dead space to tidal volume (VD/VT) was normal in all subjects.

Minute Ventilation, Alveolar Ventilation and Oxygen Consumption (Table II). Minute ventilation was increased in all subjects. As illustrated in Figure 1, this hyperventilation persisted in some instances over

a three- to five-month period. Increased oxygen consumption could be invoked as a basis for the hyperventilation only in a few subjects (increased thyroid activity in patient 9 and elevated body temperature in patient 11); in the others, no cause was apparent.

The hemoglobin concentration in eight of the patients ranged between 10 and 16.2 gm. per cent. The remaining three patients had hemoglobin concentrations of 8 to 9.6 gm. per cent. Hyperventilation was observed irrespective of the hemoglobin concentration.

Carbon Dioxide Content, Carbon Dioxide Tension (pCO₂) and pH of Arterial Blood (Table III). In the patients of the present study, the carbon dioxide content of arterial blood was low and ranged from 37 to 50 volumes per cent. This was associated with a

TABLE III

OXYGEN SATURATION, CARBON DIOXIDE CONTENT, PH, HEMATOCRIT AND PARTIAL PRESSURES FOR OXYGEN AND CARBON DIOXIDE IN ARTERIAL BLOOD

Patient No.	Oxygen Saturation (%)	Oxygen Capacity (vol. %)	Oxygen Tension (mm. Hg)	CO ₂ Content (vol. %)	CO ₂ Tension (mm. Hg)	рН	Hemato- crit (%)	Comment
1	90	14.8		40.4		7.42	32	Rest
	93	14.6		45.4			33	Rest
	94	14.8	79	38.2	24	7.40	35	Rest
2	88	11.7		39.1		7.45	23)	Rest
	94	11.7		37.1		7.45	23	Exercise
	94	10.9	71	42.5	35	7.43	25	Rest
	91	10.3	74	43.7	36	7.41	21	Rest
3	97	18.0		43.3		7.45	39)	Rest
	94	18.0		41.1			}	Exercise
	93	18.0		43.1		7.45	421	Rest
1	97	18.0		41.2			}	Exercise
1	95	18.0		43.2		7.41	42	
	91	18.3	69	42.3	32	7.43	39	Before paracentesi
	92	18.1	82	43.3	33	7.42	40	After paracentesis
4	86	15.7		48.1		7.44	34)	Rest
	88	15.7		47.4		7.43	}	Exercise
	93	15.4	94	48.7	43	7.40	31)	Rest
	95	15.4		47.1			31	35 % O2
5	94	11.5	71	42.3	36	7.42	23	Rest
6	94	17.3	74	42.7	33	7.41	23	Rest
	92	17.0	76	43.1	35	7.44	36	Rest
7	96	19.4		46.4	38	7.43	45	Rest
	95	19.4	75	47.1	37	7.40	43	Rest
	91	18.5		46.6		7.41	42)	Rest
	93	18.5		50.1		7.35	42	Before 5% CO2
8	96	13.9	73	46.4	36	7.43	31	Rest
	99	12.3	85	47.6	39	7.42	29	Rest
9	92	15.4	83	41.7	33	7.48		Rest
	93	15.4		41.7			32	Rest
10	100	15.3	100	47.6	37	7.43	33	Rest
11	94	10.8	88	38.4	32	7.42	23	Rest

Duplicate values obtained on different days, except if indicated by }. The oxygen saturation increased after either exercise or breathing 5% CO₂ in patients 2, 3, 4 and 7.

normal, or slightly elevated pH of arterial blood. The directly determined carbon dioxide tension in arterial blood ranged from 32 to 43 mm. Hg. (Fig. 2.) Normal control values for the directly determined arterial carbon dioxide tension range in our laboratory from 38 to 44 mm. Hg (mean 40 mm. Hg).

The Alveolar-Arterial Oxygen Pressure Gradient and Diffusing Capacity for Oxygen (Do2) (Table II). The oxygen tension in arterial blood remained low, despite an abnormally high alveolar oxygen tension, leading to an increased resting alveolar air to arterial blood oxygen pressure gradient (A-a gradient) in nine of the patients, ranging from 17 to 45 mm. Hg (mean 30 mm. Hg). (Fig. 3.) In only two patients was the A-a gradient normal; one of these (4) had well compensated cirrhosis of Laennec's type, the other (10) disease of the liver secondary to schistosomiasis.

The diffusing capacity for oxygen in eight patients while at rest (1-5, 6, 7 and 11) ranged from 11.2 ml./minute/mm. Hg to 23.8 ml./minute/mm. Hg with an average value of 15.6 ml./minute/mm. Hg.

Oxygen Saturation of Arterial Blood (Table III). The oxygen saturation varied considerably between subjects and between determinations in the same subject. In the face of normal diffusing capacity for oxygen, three alternate possibilities remain which could account for the low arterial oxygen content.

1. Analytical error: The analytical error in our laboratory for duplicate determinations of the oxygen content is less than 1 per cent. Reduced arterial oxygen saturation due to falsely high oxygen capacity may be caused by conversion of ferric to ferrous hemoglobin. However, the consistency of the values for oxygen capacity in any one person and the good

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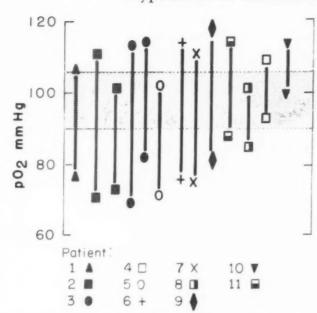


Fig. 3. The calculated alveolar oxygen tension $(P_{\Lambda_{O_2}}, upper\ dot)$ and the measured arterial oxygen tension $(P_{\Lambda_{O_2}}, lower\ dot)$ in eleven patients with cirrhosis of the liver. Each symbol represents one patient. The normal range observed in this laboratory is indicated by the shaded area.

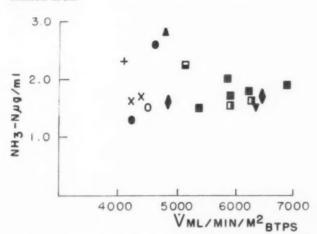


Fig. 4. Ammonia (volatile base) content of arterial blood in $\mu g./ml$. plotted against minute ventilation (\dot{V}) in ml./minute/ M^2_{BTPS} .

correlation with the predicted values obtained from the hematocrit, preclude analytical error as the major cause for variations in oxygen content.

2. Changes in the hemoglobin molecule: Changes in the hemoglobin molecule leading to decreased affinity for oxygen have been considered by Keys and Snell [3,4] as a possible mechanism. In vitro equilibration of blood with gas mixtures of known composition would exclude this possibility if the expected level of oxygenation is reached. The results of in vitro equilibration of venous blood samples of six patients (1, 2, 3, 6, 7 and 9) with oxygen unsaturation of arterial blood, are shown in Table IV. It can be seen that the expected

Table IV

A COMPARISON OF OBSERVED AND PREDICTED VALUES
FOR OXYGEN SATURATION OF BLOOD AFTER in vitro
EQUILIBRATION OF VENOUS BLOOD WITH GAS
MIXTURES OF KNOWN COMPOSITION

pН	Oxygen Saturation Predicted (%)	Oxygen Saturation Observed (%)	Oxygen Tension (mm. Hg)	Patient No.
7.4	97.5	97.4	93	1
7.3	93.4	94.0	85	2
7.4	97.0	97.2	92	3
7.3	96.5	95.9	94	6
7.4	97.0	96.8	93	7
7.3	96.0	94.0	93	9

level of oxygenation was reached in all but one instance at oxygen tensions close to the observed arterial blood oxygen tension.

3. Increased venous admixture: Increased venous admixture could account for the observed changes and this possibility will be discussed later.

The Arterial Blood Ammonia (Volatile Base) Content. The arterial blood ammonia content was increased in all patients and varied between 1.3 and 2.7 µg./ml. The normal values in our laboratory range between 0.3 and 1.0 µg./ml. Minute ventilation (V ml./minute/M²_{BTPS}) is plotted against the simultaneously determined arterial blood ammonia content in Figure 4. No apparent correlation was found between these two variables. Attempts to alter the blood ammonia level by either administration of neomycin, or by altering protein intake, failed.

COMMENTS

These studies confirm that in patients with cirrhosis of the liver hyperventilation may occur in the absence of increased oxygen consumption, anemia, fever or intrinsic pulmonary disease. The hyperventilation leads to mild, compensated respiratory alkalosis as indicated by the low carbon dioxide tension and normal, or slightly elevated pH of arterial blood. (Fig. 2.) Several possible mechanisms could cause this abnormality and will be discussed separately.

The partial pressure for oxygen in arterial blood has to be considered as a potential stimulus for the respiratory center, because the two most effective physiological stimuli, pCO₂ and pH, cannot account for the observed hyperventilation. Low arterial blood oxygen tension, despite normal or elevated alveolar oxygen tension, was found in nine out of eleven patients studied. A similar observation has been made by others [5].

Lowering of the partial pressure of oxygen in arterial blood, despite normal lung volumes and hyperventilation, may be due to one of three possible mechanisms: (1) reduced diffusing capacity for oxygen; (2) changes in the hemoglobin molecule; or (3) increased admixture of venous blood.

The diffusing capacity for oxygen, determined at rest in seven of the eleven patients, was within normal limits. This excludes reduced diffusing capacity for oxygen as a cause for the observed low oxygen tension. The alternate possibility, that the low arterial oxygen tension is due to changes in the hemoglobin molecule, as originally assumed by Keys and Snell [3,4], seems also unlikely because the expected level of saturation was obtained if venous blood of patients with unsaturated arterial blood was incubated in vitro with gas mixtures of known oxygen tensions. (Table IV.) It therefore seems most likely that the low arterial oxygen tension in cirrhosis of the liver is secondary to increased admixture of venous blood. This admixture could take place via one of three possible pathways:

1. Hypoventilation of certain segments of the lung, e.g., because of elevation of the diaphragm secondary to ascites. This could lead to increased admixture of poorly oxygenated blood via normal vascular channels. This was shown in one patient (3) Table III, in whom the arterial oxygen tension did increase following paracentesis. However, in the remaining patients low arterial oxygen tensions were observed irrespective of the presence or absence of ascites. Furthermore, duplicate determinations of the oxygen content of arterial blood on different days was frequently associated with considerable variations without changes in either ventilation, or abdominal fluid content. The normal V_D/V_T ratio and index of intrapulmonary mixing provided additional evidence that the low Pao, was presumably not due to ventilatory insufficiency.

An increased alveolar-arterial gradient for oxygen tension has been observed in patients with severe anemia and has been ascribed to relatively increased venous admixture [16]. The hemoglobin concentrations, however, of the patients in the above mentioned study were considerably less than the lowest values observed in this study. Reduced hemoglobin concentrations in cirrhosis of the liver may, furthermore, not reflect a true reduction in red cell mass but may be secondary to an increased plasma volume [6,17]. The effect of reduced hemoglobin con-

centration secondary to blood loss may not be comparable to reduced hemoglobin concentration because of increased plasma volume.

2. Multiple intrapulmonary arteriovenous communications, which have been observed in one patient with juvenile cirrhosis of the liver [18]. This led to marked oxygen unsaturation, secondary polycythemia and a clinical syndrome resembling a congenital lesion of the heart. No such arteriovenous communications are known to exist in adults with Laennec's type of cirrhosis.

3. Venous communications between the portal vascular bed and periesophageal, mediastinal, bronchial and pulmonary veins, which have been reported in patients with cirrhosis of the liver [10]. It is conceivable that these communications may lead to considerable shunting of blood. A shunt of unknown localization between venous and arterial blood has previously been postulated in patients with cirrhosis of the liver [19], because of the high alveolar-arterial oxygen pressure gradient during the administration of 100 per cent oxygen. No attempts were made in this study to obtain mixed venous blood for either measurement of the cardiac output or calculation of the volume of blood shunted. An approximate value, however, for the magnitude of the shunt can be calculated as a fraction of the simultaneous cardiac output (Qva/Qt) from the available alveolar, i.e., end-capillary and arterial blood oxygen tension, assuming a membrane component of less than 1 mm. Hg and a difference in oxygen content between arterial (endcapillary) and mixed venous blood of 20 per cent. The Qva/Qt ratio calculated in this manner ranged from 6 to 32 per cent. The true values for the volume of the shunt are probably even larger, because of the relatively higher oxygen content of portal blood, if, as is suspected, the admixture of venous blood originates in the portal vasculature. Variations in the amount of blood which is shunted could account for the variability in the oxygen content of arterial blood between determinations in the same person. (Table III.) It is therefore conceivable that the volume of flow in anastomoses between two venous vascular beds (portal vein and pulmonary vein) requires only a low pressure gradient, so that it is easily affected by respiration and variations in intra-abdominal pressure and splanchnic blood flow.

The mechanism maintaining hyperventilation in the presence of a low pCO₂ and normal, or slightly elevated pH, remains obscure. The

observed oxygen unsaturation of arterial blood, i.e., the low oxygen tension, was not of the order of magnitude commonly assumed to be necessary for stimulation of the respiratory center [7]. Because none of the known physiological stimuli can account for the observed hyperventilation in cirrhosis of the liver, other non-physiological stimuli have to be considered. Roberts, Thompson, Poppel and Vanamee [1,8] have related hyperventilation to the elevated blood ammonia level. The poor correlation between the blood ammonia (volatile base) content and minute ventilation, also observed in this study (Fig. 4), was explained by additional variables such as the pH of blood. It is conceivable that not the absolute concentration of ammonia, but the ratio of diffusable ammonia to non-diffusable ammonium ions, determines the stimulatory effect [20]. Diffusion of ammonia is known to be affected by differences in pH [21,22] and an increased gradient for hydrogen ions between the blood and the intracellular compartment would facilitate such diffusion. The "toxicity" of ammonia (ammonium ion) is also determined by the nature of the accompanying anion [23]. Thus, while ammonia cannot be excluded as a potential stimulus for "primary" hyperventilation, other, presently not identified metabolites, such as primary amines, some of which are known to have marked pharmacological action, should also be considered [24]. Metabolites originating in the intestinal tract could gain direct entrance into the systemic arterial circulation via the previously mentioned abnormal vascular communications. That such a pathway is taken by intestinal metabolites in patients with cirrhosis of the liver seems to be confirmed by the observation that the ammonia content of arterial blood may exceed that of mixed venous blood [25].

The increased minute ventilation may also be due to a reflex, initiated by changes in the elastic properties of the lung parenchyma, a mechanism previously postulated in patients with mitral stenosis to explain the observed hyperpnea [26]. Such changes in cirrhosis of the liver may be due to an increased central blood volume, because a considerable volume of blood has to be shunteb via the periesophageal veins into the pulmonary veins to account for the observed low PAO₃.

SUMMARY

1. Low arterial oxygen tension and hyperventilation was shown to be present simul-FEBRUARY, 1960 taneously in patients with cirrhosis of the liver.

2. The low arterial oxygen tension is best explained by assuming portal to pulmonary vein anastomoses.

3. The mechanism causing "primary" hyperventilation remains unexplained.

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Coincidence of Patent Ductus Arteriosus and Rheumatic Heart Disease, with a Comment on the "Postcommissurotomy Syndrome"

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THE frequent occurrence of rheumatic heart disease in patients with hearts showing interatrial septal defects is now fairly well known, and a few references to its presence with other congenital anomalies have appeared. Roesler [1] collected reports on sixty-two patients with interatrial septal defect, forty-eight of whom (77.4 per cent) showed postmortem evidence of chronic valvular lesions affecting one or more valves. Taussig and others [2] described four patients showing a similar coincidence. Gelfman and Levine [3] in 181 hearts with congenital defects found twenty-five (14 per cent) with superimposed rheumatic infection. In this series rheumatic infection was found in association with bicuspid aortic valve in eight; interatrial septal defect in five; two each among interventricular septal defect, quadricuspid aortic valve, coarctation of the aorta, and accessory septums; and one each among patent ductus arteriosus, bicuspid pulmonic valve, pulmonic stenosis and tetralogy of Fallot. Durlacher and Beyer [4] described twenty-two patients with rheumatic lesions among fifty-five autopsy patients showing congenital malformation of the heart, four of the twenty-two having active rheumatic myocarditis at the time of death. The rheumatic lesions occurred in four of six cases of interauricular septal defect, two of four cases of tetralogy of Fallot, two of four cases of interventricular septal defect, one of three cases of truncus arteriosus, two of six cases of patent ductus arteriosus, and in eleven of twentynine minor malformations. Other isolated reports of single cases have appeared.

The reported occurrence of rheumatic fever associated with patent ductus arteriosus, all

based on postmortem findings, may be no more than might be expected on the basis of chance coincidence. We reviewed the records of the pathology department of the Medical College of South Carolina for the past twenty years, and found only four autopsy cases in which patent ductus arteriosus was found in patients over two years of age, none with rheumatic lesions.

We have been impressed, however, by the number of cases of clinically diagnosed rheumatic heart disease appearing during the follow-up period in our patients operated upon for cure of patent ductus arteriosus. Through the year 1957 we had operated upon a total of seventy-three patients, thirty-six of whom we were able to examine periodically following operation. Of the thirty-six patients with adequate follow-up, four are thought to have definite rheumatic heart disease, and two more probably have it.

CASE REPORTS

Case I. A three and a half year old Negro female (A-1998) had a history of frequent infection of the upper respiratory tract but no symptoms suggesting rheumatic fever. Physical examination, x-ray studies and right heart catheterization findings were typical of patent ductus arteriosus. On May 21, 1951 operation was performed, with multiple ligation of the ductus. The postoperative course was uneventful, no heart murmur being present until the fifth day, when a soft systolic murmur was heard along the upper left sternal border.

She was next seen in our Heart Clinic in March 1953 with the story that she had been asymptomatic and had gained weight. On physical examination a rather loud, grade 2 systolic murmur was heard, best in the third intercostal space in the left para-

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sternal line. No diastolic murmur was heard, the pulmonic second sound was thought to be accentuated, and the blood pressure was 110/70 mm. Hg. She was seen again in April 1954, still asymptomatic, and physical findings remained essentially unchanged.

The next visit to our clinic was in April 1955, with the history of a migratory polyarthritis of ten days' duration occurring one month previously. The temperature was 99.6°F. The heart showed tachycardia, the previously described parasternal systolic murmur and accentuated pulmonic second sound, and in addition an apical diastolic rumble ending in a snapping first sound. The erythrocyte sedimentation rate (Wintrobe) was 38 mm./hour. She was admitted to the hospital with a diagnosis of active rheumatic fever. In the hospital the antistreptolysin-O titer rose from 1:512 to 1:1024. The C-reactive protein test was negative. A throat culture for beta-hemolytic streptococcus was positive. The electrocardiogram which had previously shown left axis deviation now showed possible right ventricular hypertrophy. Evidence of rheumatic activity gradually receded under salicylate and cortisone therapy.

In June 1955 a second right heart catheterization was performed. No evidence of left-to-right shunt of blood was found at any level. The pressure in the right main pulmonary artery was 50/25 mm. Hg, and in the right ventricle 65/0 mm. Hg. The heart murmurs persisted, and in the light of the cardiac catheterization, findings were considered to be diagnostic of mitral stenosis and insufficiency. Shortly afterward, the patient's family moved to Philadelphia, and attempts to obtain further information about her course have been unsuccessful.

CASE II. A thirteen year old white female (A-28918) had spent several months in a convalescent home for rheumatic fever; she was sent to us in July 1953 with the opinion that her predominant difficulty was congenital heart disease. The physical examination, x-ray studies and right heart catheterization findings were typical of patent ductus arteriosus. The systemic blood pressure was 105/60 mm. Hg. On November 30, 1953, operation was performed, with ligation and division of a large patent ductus arteriosus. Immediately following operation no murmurs were heard over the precordium. The postoperative course was accompanied by high fever for the first four days, and on the fifth day a rather loud systolic murmur and a faint diastolic murmur were described over the aortic area. The fever was considered to be possibly on the basis of a penicillin sensitivity and there was no agreement on the significance of the aortic murmurs.

Following discontinuance of penicillin the fever subsided after a few days and the remaining course was uneventful except for persistence of the murmurs. A follow-up clinic visit in January 1954 showed only a loud systolic murmur at the aortic valve area; the

blood pressure was 110/85 mm. Hg. Similar findings were noted on monthly clinic visits until July 1954 when the blood pressure was found to be 80/70 mm. Hg. Subsequent monthly visits disclosed the patient to be asymptomatic but the low systemic blood pressure and the loud systolic aortic murmur persisted.

The possibilities of additional undiscovered congenital defects, and of recanalization of the ligated ductus arteriosus were considered as likely explanations for the murmur, and to investigate these possibilities she was again subjected to right heart catheterization in October 1954. Normal pressures and no evidence of left-to-right shunt were found at all levels of the catheter tip. Aortic valve disease was then considered as the best explanation for both the murmur and the blood pressure change. Because of the absence of a murmur in the first few postoperative days and its appearance following a febrile episode, and the subsequent narrowing of the pulse pressure, it was thought to be more likely of rheumatic than congenital origin.

In March 1956 the patient was in bed at home for four weeks with acute glomerulonephritis. In July 1956, a grade 2 apical systolic murmur was noted in addition to the aortic systolic murmur. In May 1957, the addition of a faint aortic diastolic murmur was noted, and this combination of murmurs was still present in May 1958. The patient was now considered to have progressive rheumatic involvement of mitral and aortic valves, and because of sensitivity to penicillin, prophylactic sulfadiazine therapy was prescribed.

CASE III. A nine year old Negro female (A-2777) came to our clinic in June 1951. The history disclosed knowledge of a heart murmur since infancy. There were frequent episodes of tonsillitis, and in the past few months repeated episodes of severe epistaxis. Physical examination and right heart catheterization findings were typical of patent ductus arteriosus. Operation was performed on June 26, 1951, with multiple ligation of the ductus. Immediately after operation no murmur could be heard over the precordium, but twenty-four hours later a faint systolic murmur was noted at the aortic valve area. By the time of discharge from the hospital the murmur had increased to grade 2 or 3 intensity, although the postoperative course was otherwise uneventful.

The patient was followed regularly in the clinic, and no change was noted in the physical findings until April 1957, when a faint, high pitched diastolic murmur was heard along the upper left sternal border, and the blood pressure was found to be 130/70 mm. Hg. On subsequent visits the diastolic murmur became more definite and the increase in pulse pressure persisted. There had been no symptoms since operation which suggested rheumatic fever, and recanalization of the ductus was suspected. Right heart catheterization was again performed in October 1957, with the finding of normal pressures and no evidence of left-to-right shunt at any level of the catheter tip.

At this time the corrected erythrocyte sedimentation rate (Wintrobe) was 34 mm./hour and the test for C-reactive protein was negative.

It was concluded that the patient had superimposed rheumatic involvement of the aortic valve, and prophylactic Bicillin® therapy was prescribed.

Case IV. A seventeen months old Negro female (A-56120) had a history of increasing dyspnea on exertion and frequent respiratory infections since the age of eight months. Two months previously she had had a profuse spontaneous epistaxis. Physical examination revealed marked cardiomegaly, a loud grade 3 midprecordial systolic murmur, blood pressure of 100/40 mm. Hg, and signs of early congestive heart failure. The signs of congestive failure disappeared following digitalization, and in June 1956 both right heart catheterization and retrograde aortograms demonstrated evidence of a large patent ductus arteriosus.

In August 1956 operation was performed, with ligation and division of the ductus arteriosus. No heart murmurs were audible for three days following operation, but on the fourth day a high pitched grade 2 systolic murmur was noted to be present near the apex and to be well transmitted out into the left axillary line. Convalescence was otherwise uneventful. Both the heart size and the increased pulmonary vascular markings showed definite decrease on roentgenograms taken before discharge from the hospital. Maintenance of digitalis and monthly prophylactic Bicillin therapy was recommended, but these drugs were given only irregularly at home.

She was seen in our heart clinic at three-to-six-month intervals, her grade 2 apical systolic murmur being present on each occasion. In June 1957 the mother reported that the child had shown a poor appetite and had been having nocturnal fever. In January 1958 the mother reported frequent colds, nosebleeds and occasionally painful ankles. At this visit the general physical findings were unchanged, but the corrected erythrocyte sedimentation rate (Wintrobe) was 24 mm./hour, and the antistreptolysin-O titer was 1:2560. She was given 1.2 million units of Bicillin intramuscularly at each visit to our clinic, but it is unlikely that any other medication was received at home.

At her last visit in May 1958 the mother reported no complaints. The grade 2 apical systolic murmur was again present. The corrected erythrocyte sedimentation rate (Wintrobe) was 8 mm./hour and a throat culture for beta-hemolytic streptococcus was reported negative.

Case v. A four year old white female (A-29063) had been known to have a heart murmur since shortly after birth. During the previous year she had spontaneous nosebleeds every two to three months, but no other symptoms suggesting rheumatic fever. Physical

examination, x-ray studies and right heart catheterization findings were typical of patent ductus arteriosus. Operation was performed in June 1954 with multiple ligation of the ductus arteriosus. No murmur could be heard immediately following operation. Eight hours after operation the temperature was 102°F., remained between 100° and 102°F. for twenty-four hours, between 99.5° and 101.5°F. for another forty-eight hours, and was subsequently within the normal range. A pericardial friction rub was audible the day following operation, and was last heard on the eighth postoperative day, when a loud, grade 3 systolic murmur was first noted, of maximal intensity in the apical region, with wide radiation. The remainder of her course was unchanged, and the apical systolic murmur was still present when she left the hospital on the twelfth day following operation

The murmur persisted at subsequent clinic visits. In July 1954 it was described as grade 3, and prophylactic Bicillin therapy was prescribed to be taken orally. Frequent colds accompanied by nosebleeds were the only symptoms suggestive of rheumatic fever activity. She was next seen in September 1957, and the murmur had decreased in intensity to grade 2. She was referred to the rheumatic fever clinic for subsequent follow-up visits.

CASE VI. A six year old white male (A-57670) had a history of turning blue on coughing or crying from soon after birth until the age of two or three years. A diagnosis of patent ductus arteriosus was made at the the age of 5 months by an internist in Atlanta, Georgia. No more cyanosis was noted after the age of two or three years, but physical development lagged somewhat behind that of his siblings, he tired more easily and was subject to more frequent and severe infections of the upper respiratory tract. No symptoms suggestive of rheumatic fever were elicited. Findings on physical examination included the typical murmur of patent ductus arteriosus, and blood pressure in the right arm of 112/40 mm. Hg. Several observers noted a decrease in the pulses of the lower extremities, but no measurement of blood pressure in the legs was recorded. The diagnosis was patent ductus arteriosus and possible mild coarctation of the aorta. Right heart catheterization was not performed.

Operation was not performed.

Operation was performed in August 1956 with division and ligation of a ductus arteriosus 5 mm. in diameter and 8 mm. in length. A moderate coarctation of the aorta was present at the level of the ductus, the lumen of this being estimated to be 1 cm. in diameter. After some deliberation and consultation, it was decided not to resect the coarctation. Immediately following operation a grade 2 systolic murmur was heard in the second and third intercostal spaces in the left parasternal line. The day following operation the murmur had disappeared. On the fourth and fifth postoperative days the temperature rose to 100°F. but subsequently remained normal. On the sixth and

seventh postoperative days the murmur reappeared, but was not heard subsequently. He was discharged from the hospital on the tenth postoperative day.

The patient was seen in the heart clinic in November 1956, and had remained asymptomatic. A grade 1, faint systolic murmur was audible in the pulmonary valve area. A third heart sound was heard at the apex. The blood pressure in the right arm was 118/70 mm. Hg. Prophylactic Bicillin therapy was recommended for the winter months. He was again seen in May 1957, and similar findings were noted. Bicillin prophylaxis was discontinued.

The next clinic visit was in November 1957. No complaints were recorded. Examination of the heart disclosed a grade 2 systolic murmur audible over the entire precordium with transmission to the left axilla, and a third heart sound in diastole at the apex. The corrected erythrocyte sedimentation rate (Wintrobe) was 16 mm./hour and the test for C-reactive protein was positive 2 mm. Bicillin prophylaxis was reinstituted.

At the next visit in March 1958 the cardiac findings were unchanged and a louder murmur with transmission to the axilla was also heard on the last visit in July 1958 At this time the corrected erythrocyte sedimentation rate (Wintrobe) was 11 mm./hour.

COMMENTS

It is obvious that in the presence of the usually loud "machinery" murmur of patent ductus arteriosus, the characteristic murmurs of coexisting rheumatic heart disease can easily be overlooked. Persisting murmurs after operation may also be caused by other undiscovered congenital heart defects. But the appearance of clinically active rheumatic fever and clinically progressive valve disease in the patients herein described have led us to believe that they may have a previously unsuspected susceptibility to rheumatic infection. No one has satisfactorily explained the well known association between atrial septal defects and rheumatic valvular disease. Moreover, the series reported by Gelfman and Levine and by Durlacher and Beyer showed a fairly wide distribution of rheumatic lesions in hearts with a variety of congenital defects. It does not seem unlikely to us that there may be decreased resistance to rheumatic infection in all congenital heart anomalies.

Ito, Engle and Goldberg [5] have called attention to a "postpericardiotomy syndrome" following intrapericardial surgery of congenital heart disease, resembling in all respects the "postcommissurotomy syndrome" considered by some to represent reactivation of rheumatic fever. They indicated that the feature common

to both was wide incision of the pericardium and that a traumatic pericarditis was probably responsible in each syndrome, since their patients presumably were free of rheumatic infection. If, however, patients with congenital heart lesions have an increased susceptibility to rheumatic fever, the appearance of this puzzling syndrome in the patients described by Ito, Engle and Goldberg might instead be construed as further evidence that the "postcommissurotomy syndrome" is a reactivation of rheumatic fever, the common factor being operative trauma or postoperative infection as the precipitating event.

The practical implication of this study in the management of patients with congenital heart lesions seems to us to be that it may be as desirable to use antibiotic prophylaxis in them as in those with rheumatic fever. Since bacterial respiratory infections, bacterial endocarditis, and probably rheumatic infection develop frequently in many such patients, routine prophylaxis such as is carried out in rheumatic fever should be beneficial. If reactivation of rheumatic fever by operative procedures is as frequent an occurrence following surgical treatment of congenital heart defects as our study suggests, postoperative follow-up in these patients should be regular and prolonged, and ideally should include participation of a physician skilled in the detection and management of rheumatic fever.

SUMMARY

Among a total of seventy-three patients operated upon for patent ductus arteriosus, thirty-six had adequate observation over a period of two to seven years following operation. Of the thirty-six patients, clinical evidence of rheumatic fever or a progressive valvular disease has developed in six. The study suggests a more frequent association between patent ductus arteriosus and rheumatic heart disease than has been previously suspected, and in some cases operation may have either precipitated or reactivated rheumatic fever.

The possible significance of these findings in relation to the etiology of the "postcommissurotomy syndrome" is discussed. The suggestion is made that long term observation following operation for congenital heart defects should include special attention to the possibility of the occurrence of superimposed rheumatic fever.

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Chronic Active Pulmonary Histoplasmosis with Cavitation*

A Clinical and Laboratory Study of Thirteen Cases

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HISTOPLASMOSIS is a disease caused by the fungus, Histoplasma capsulatum [1,2]. It is acquired by inhalation of the spores of this organism which grows saprophytically in nature [3-5]. Propagation is fostered in localized areas in which microclimatic conditions of temperature and humidity are favorable [6]. As late as 1945, histoplasmosis was generally considered to be a fatal illness [7,8]. Soon thereafter, studies of pulmonary calcifications in roentgenograms of negative tuberculin skin reactors gradually changed the concept of the disease spectrum [9-11]. Several recent studies, employing the histoplasmin skin test as an epidemiologic tool, have shown that the fungus has a worldwide distribution [12] with a high prevalence in the midwestern United States [13-14]. In the United States alone, approximately 30 million people, living particularly in the north central and south central states, have experienced some form of histoplasma infection [15]. The investigation of epidemic outbreaks of unusual forms of pneumonias [16-24] and cases of acute respiratory tract infections [25] with the histoplasmin skin test, complement fixation test and culture technics have established clearly the histoplasma fungus to be the etiologic agent of a variety of clinically apparent, as well as inapparent, respiratory infections [16,17,26-33].

Histoplasma infections fall generally into the following three categories: (1) the clinically inapparent infections associated with pulmonary calcification and detected by the skin test, com-

prising the largest group; (2) the clinically recognized acute and chronic febrile illnesses associated with pulmonary consolidation, occurring singly or in groups of individuals, and detected by use of all the diagnostic procedures previously mentioned; and (3) the fatal cases in which lesions of the mucous membranes and systemic involvement are present [15,16,27,34–36].

Acute and chronic pulmonary histoplasmosis often cannot be distinguished clinically or roentgenographically from tuberculosis. In particular, many patients with pulmonary cavitation due to histoplasmosis occurring in areas of high endemicity for the disease are referred to and admitted to sanatoriums for treatment and care. During the past several years an increasing number of patients admitted to tuberculosis sanatoriums have been recognized as having histoplasmosis through the use of the histoplasmin skin test, the complement fixation test for the detection of histoplasma antibodies and special cultural procedures for isolation of the histoplasma fungus [37,38]. It has been estimated that about 1,200 such cases are undiagnosed in tuberculosis sanatoriums in the central United States at present [39].

Since 1949, thirteen cases of chronic active pulmonary histoplasmosis with cavitation have been recognized and the patients followed up from eighteen months to over eight years at the Macon County Tuberculosis Sanatorium, Decatur, Illinois. Macon County is in a geographical area in which there is a prevalence of positive

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results to the histoplasmin skin test [40]. Our clinical and laboratory experience with these cases is the subject of this report. In addition, a review of seventy-three similar cases which have been reported in the literature will be made.

MATERIALS AND METHODS

Skin Tests. Old tuberculin, usually in a dilution of 1:1,000, was applied to the ventral surface of the forearm and the reaction interpreted after forty-eight to seventy-two hours. Histoplasmin,* a sterile filtrate of a broth culture of H. capsulatum, was applied by inoculating 0.1 ml. of a 1:100 dilution intradermally in the same area on the opposite arm [41–43]. A positive reaction with either antigen is characterized by the development of an area of induration, 5 mm. or larger, surrounded by a zone of erythema of varying diameters at the site of inoculation.

Complement Fixation Test. Precipitins [44], collodion [45] and histoplasmin-latex [46,47] agglutinations, and complement fixation [48-51] tests have been employed to detect antibodies to the histoplasma fungus [42]. The complement fixation test, using an inactivated whole yeast phase suspension of H. capsulatum as antigen, has been most frequently employed. The modified Kolmer procedure utilizing a heat-inactivated whole yeast antigen has been used throughout this study. The period of incubation was fifteen to eighteen hours at 4°C., and the titer of the serum was read as the highest dilution producing 50 per cent inhibition of hemolysis. With the exception of a few at the beginning of the study, all complement fixation tests were performed in our laboratory at the University of Chicago Clinics. Once a patient was suspected of having histoplasmosis, serologic studies were performed periodically for detection of the complement fixing antibodies to the histoplasma fungus, and for recording their persistence in positive reactors.

Cultural Procedure. H. capsulatum is not a fastidious organism and will grow on a variety of laboratory media [52–54]. At the beginning of the study a few sputum specimens were sent for culture to the Illinois Public Health Department or the U. S. Public Health Service Laboratory at Chamblee, Georgia. Many sputum specimens were submitted to the laboratory at the University of Chicago for direct culture and

* Obtained from Parke, Davis and Company and Eli Lilly and Company.

mouse inoculation. Soon after the study began, direct cultural procedures, similar to those employed at the University of Chicago, were provided at the Macon County Tuberculosis Sanatorium. The media employed included cysteine-dextrose-enriched blood agar, Sabouraud's medium and corn meal agar. In some cases duplicate sputum samples were sent to the University of Chicago to be cultured for fungi.

Examination of sputum for tubercle bacilli by smear, culture and guinea pig inoculation was carried out at the Sanatorium.

All cultures for the histoplasma fungus were observed for six weeks or longer before being discarded as negative [16]. Culturing on enriched blood agar has yielded the greatest number of positive histoplasma cultures. On blood agar, H. capsulatum grows as grayish brown mucoid colonies, cerebriform in appearance. Positive cultures grown at room temperature usually will not show colonies present before ten days following inoculation. For positive identification of the fungus, colonies grown on blood agar were transferred to corn meal and Sabouraud's medium to detect the characteristic macroconidia [35].

The white laboratory mouse is highly susceptible to H. capsulatum, and the mouse inoculation technic may yield the organism from sputum when direct culturing fails. For such animal isolation, sputum was treated with penicillin (40 units per ml.) and streptomycin (80 units per ml.) and inoculated intraperitoneally into mice. After four to six weeks the animals were sacrificed. The livers and spleens were pooled, minced and spread liberally on blood agar and corn meal agar. If the sputum contains the histoplasma fungus, characteristic colonies make their appearance on the culture media after incubation for two to four weeks at room temperature.

CASE REPORTS

Space will not permit a detailed analysis of the thirteen cases reviewed in this report. Certain details which appear to characterize the history as well as the clinical and laboratory findings in cases of chronic cavitary histoplasmosis are given. All thirteen patients described were initially seen and followed up by one of us (D. F. L.) at the Macon County Tuberculosis Sanatorium. The patients subjected to surgery were referred to the University of Chicago Clinics where Dr. William Adams, Professor of

TABLE 1
ACTIVE CHRONIC CAVITARY HISTOPLASMOSIS—VITAL DATA

Case No.	Sex, Age (yr.)	Date (First Visit)	Birthplace	Residence (major)	Occupation	Detection Source
1	M, 59	5/4/49	Macon Co., Ill.	Piatt and Macon Co., 57 yr.	Farmer, mechanic	TBC Board
2	M, 50	10/4/49	Macon Co., Ill.	Macon Co., 50 yr.	Businessman	Mass survey
2 3	F, 75	3/20/51	Douglas Co., Ill.	Macon Co., 58 yr.	Housewife	Family physician
4	M, 49	5/28/51	Cook Co., Ill.	Cook Co., 25 yr., Madison Co., 20 yr.	Railroad oiler, salesman	TBC Board
5	M, 62	11/10/51	Tippecanoe Co., Ind.	Macon Co., 36 yr.	Railroad engineer	Mass survey
6	M, 70	6/27/53	Fayette Co., Ill.	Fayette Co., 67 yr.	Farmer	Family physician
7	M, 47	11/9/53	Edwards-White Co., Ill.	Macon Co., 30 yr.	Railroad yard clerk	Mass survey
8	M, 67	6/20/55	Fayette Co., Ill.	Fayette Co., 67 yr.	Railroad conductor	Mass survey
9	M, 58	9/26/55	Douglas Co., Ill.	Douglas Co., 25 yr.	Pipe fitter, factory worker	Mass survey
10	M, 52	10/29/55	Christian Co., Ill.	Macon Co., 38 yr.	Print shop owner	Mass survey
11	M, 48	5/20/56	Coles Co., Ill.	Coles Co., 44 yr.	Landscape gardener	Family physician
12	M, 58	9/19/56	Fayette Co., Ill.	Fayette Co., 26 yr. Macon Co., 15 yr.,	Laborer, janitor, roofer, farmer	Family physician
13	M, 50	11/16/56	Piatt Co., Ill.	Piatt Co., 50 yr.	Farmer	Mass survey

Surgery, or his associate, Dr. Peter Moulder, Associate Professor of Surgery, performed the operative procedure. Dr. Eleanor Humphreys, Professor of Pathology, provided us with the opportunity to examine histologically and culture the surgical specimens for the presence of H. capsulatum.

Case I. W. W., a fifty-nine year old white man, was admitted on May 4, 1949. He was born in Macon County and had lived there or in adjoining Piatt County all his life. (Table I.) He had worked on a farm until the age of seventeen. After twenty months of military service, during World War I, he had operated a garage until 1935. He returned to farming for the next seven years. From 1942 to May 1946 he worked as a mechanic for the Caterpillar Military Engine Company in Decatur, Illinois.

His present illness began in early June 1947, 23 an insidious febrile illness, diagnosed as pneumonia and treated with penicillin. When the lesion did not clear, tuberculosis was suspected and the patient was admitted to the V. A. Hospital at Outwood, Kentucky, on June 17, 1947. He remained there for three months. A summary of the hospital record reveals that he appeared chronically ill, had a productive cough, and weighed 102 pounds. A chest roentgenogram showed infiltration with cavitation in the upper lobe of the right lung; the left lung was clear. Marked emphysema was present. The result of a sputum examination for pyogenic organisms, tubercle bacilli and fungi was negative. The patient seemingly improved clinically

with penicillin therapy, although the chest lesion remained unchanged. When lobectomy was recommended, the patient left the hospital against advice. The diagnosis at the time of discharge was pulmonary abscess, emphysema and malnutrition probably due to tuberculosis.

On May 4, 1949, the patient was referred to the Macon County Tuberculosis Sanatorium by the Piatt County Tuberculosis Board with a diagnosis of pulmonary tuberculosis. His mother had died of tuberculosis in 1898. History revealed that since his attack of pneumonia in 1947 he had continued to have malaise, but no fever. Cough, productive of a slightly purulent but non-foul sputum, was present. At the time of this admission he weighed 109 pounds and complained of dyspnea and fatigue. He appeared poorly nourished and chronically ill. There were no lesions of the skin or mucous membranes. The chest expanded symmetrically. There were no localizing signs of pulmonary abnormalities and no rales were heard. The heart sounds were normal. The blood pressure was 106 mm. Hg systolic and 70 mm. Hg diastolic. There was no lymphadenopathy or enlargement of the liver and spleen. Sputum cultures again were negative for tubercle bacilli and fungi. The roentgenogram of the chest still showed right apical infiltration with cavitary formation and bilateral emphysema. (Fig. 1A.) A diagnosis of pulmonary tuberculosis was made. He gained 10 pounds while in the hospital. On discharge he continued to have

The patient was readmitted to the Macon County Tuberculosis Sanatorium on June 2, 1951. He was

AMERICAN JOURNAL OF MEDICINE

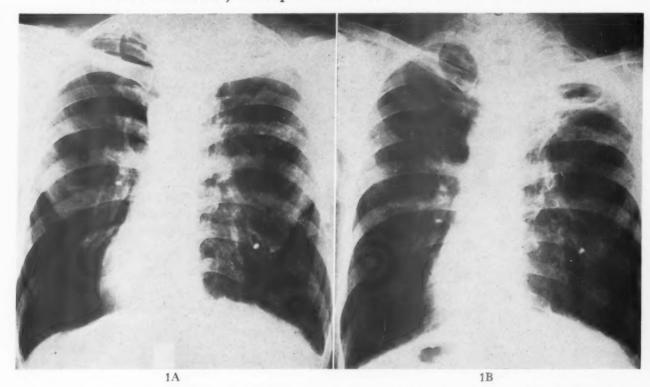


Fig. 1. Case i. A, chest roentgenogram taken May 4, 1949, showing bilateral emphysema, calcification and right apical infiltration with cavitation. B, chest roentgenogram taken June 9, 1952, showing enlargement of right apical cavitary lesion and bilateral emphysema. These and the subsequent films are anteroposterior views.

acutely ill with fever, sweating, rapid respirations and pulse. There was cough productive of yellow sputum. Roentgenographic examination showed that the right apical infiltration had increased. A tentative diagnosis of moderately advanced tuberculosis was made, but pulmonary abscess of the upper lobe of the right lung was also considered. On inquiry it was found that his aunt (P. B., Case III of this series) had pulmonary histoplasmosis. Physical examination was essentially the same as on the first admission. There

was some immobility of the right side of the chest on expansion. Amphoric breathing in the apical region of the right side of the chest associated with scattered rales was present. The left lung appeared normal. The heart was normal. The blood pressure was 102 mm. Hg systolic and 72 mm. Hg diastolic. There were no lesions of the skin or mucous membranes and the abdomen showed no abnormalities. The liver, spleen and lymph nodes were not enlarged. The clinical and laboratory findings are shown in Tables II

Table II
ACTIVE CHRONIC CAVITARY HISTOPLASMOSIS—SYMPTOMS

						C	Case No.						
Symptoms	1	2	3	4	5	6	7	8	9	10	11	12	13
Anorexia Tatigue	++++	-	++++	++++	++++	+++	++	+ -	=		+++++	- + +	-
ever	++	-	+	+	=	+	_	_	_	_	++	=	=
Chills Oyspnea Wheeze	++	_	+	++++	- +	++	+	-+	_	=	+	++	=
Chest pain	++	+	++	++++	+++	++	++	+++	++	+	+++	+++	+
Expectoration	++	+ - +	++	++++	++++	++	++	++++++	+ -	+	++	+++++	+
Purulent sputum	-	_	_	+++	+++	_	-	-	_	_	_	-	-

Table III

ACTIVE CHRONIC CAVITARY HISTOPLASMOSIS—HISTORY, PHYSICAL AND LABORATORY FINDINGS*

	Dura-				Red Blood		White Blood	Diffe	erentia	al (%)		
No. First Visit	tion before First Visit (mo.)	Tuber- culous Contacts	Weight Loss (lb.)	Chest X-ray Findings	Cells (mil- lion per cu. mm.)	Hemo- globin (gm.) %	Cells (thous- and per cu. mm.)	Polymorpho- nuclear leukocytes	Lymphocytes	Monocytes	Eosinophils	Sedimen- tation Rate (mm./hr.)	Urinalysis
1	23	1	18	Right upper lobe infiltration and cavitation	4.8	13.5	7.5	61	35	3	1	22	Negative
2	1	1	None	Bilateral infiltration and cavi-	5.0	15.4	11.0	72	23	2	3	17	Negative
3	1	5	5	Left upper lobe cavitation	4.7	15.8	8.0	60	36	2	2	8	Negative
4	25	1	11	Bilateral infiltration and cavi- tation	5.2	14.0	8.2	60	39	0	1	18	Negative
5	6	1	17	Right upper lobe infiltration and cavitation	4.6	12.2	7.2	64	26	9	1	26	Negative
6	24	2	14	Bilateral infiltration and cavi- tation	4.3	13.1	6.9	63	35	0	2	10	Negative
7	7	7	25	Right upper lobe infiltration and cavitation	4.2	13.9	9.0	63	28	6	3	20	Negative
8	30	1	14	Left upper lobe cavitation, right upper lobe infiltration	3.7	11.6	7.8	65	30	5	0	25	Negative
9	3	None	12	Left upper lobe infiltration and cavitation	5.3	15.0	13.2	63	34	2	1	15	Negative
10	3	1	None	Left upper lobe infiltration and cavitation	4.0	13.6	7.0	52	46	2	0	18	Negative
11	12	1	8	Bilateral infiltration, left upper lobe cavitation	4.3	14.0	11.7	83	14	1	2	16	Negative
12	16 yr.	None	10	Right upper lobe infiltration and cavitation	4.4	14.5	7.3	50	45	1	4	20	Negative
13	6	None	None	Left upper lobe infiltration and cavtation	4.5	13.5	6.0	48	50	2	0	21	Negative

^{*}Skin or mucous membrane lesions, enlarged spleen or liver or lymph nodes were not present.

Table IV
ACTIVE CHRONIC CAVITARY HISTOPLASMOSIS—SKIN TESTS, CULTURES AND SEROLOGY

					Tub	ercle Bacilli	i			
Case No.	Skin '	Γests *	Smear		Cu	lture		ea Pig ulation	H. capsulatum	Initial C.F. Test†
	Т	Н	Positive	Negative	Positive	Negative	Positive	Negative	Positive Culture	
1	Positive	Positive	0	82	0	6			9	1:40
2	Positive	Positive	0	96	0	13	0	3	4	1:160
3	Positive	Positive	0	26	0	10	0	1	5	neg.
4	Positive	Positive	0	53	0	14	0	3	16	1:8
5	Negative	Positive	0	36	0	10	0	1	8	1:64
6	Positive	Positive	8	97	0	22	0	2	10	1:64
7	Positive	Positive	0	34	0	8	0	1	4	1:64
8	Positive	Positive	0	27	0	27	0	2 2	8	1:256
9	Positive	Positive	4	18	0	15	0	2	8	1:128
10	Positive	Positive	0	9	0	5			10	1:256
11	Positive	Positive	0	4	0	4			5	1:16
12	Positive	Positive	0	8	0	8			9	1:16
13	Positive	Positive	0	29	0	28			10	1:2

^{*} T = tuberculin, OT, 0.1 ml. of 1/1,000 dilution. H = histoplasmin, 0.1 ml. of 1/100 or 1/1,000 dilution. † Final dilution of serum showing 50 per cent inhibition of hemolysis using heat-inactivated whole yeast antigen.

Table v

ACTIVE CHRONIC CAVITARY HISTOPLASMOSIS—SERIAL COMPLEMENT FIXATION TESTS

Time after				Case	es and l	Date of	Initial 1	Positive	X-ray				
First X-ray Evidence (yr.)	1* 6/47	2 9/49	3† 3/51	4 4/50	5‡ 6/51	6 6/53	7§ 8/53	8 11/52	9¶ 7/55	10 8/55	11 5/56	12** 6/43	13†1
0 mo.											16		
2 mo.						2.2				256	8		
4 mo.		160				* *			128	128			
6 mo.	-6.6		*****			64	64						2
8 mo.		Positive	Negative						32	128			2
10 mo.		*****							8				4
1						32	32		8	16			4
134						32	32		4				
112				8		64	16		2	32			4
134						64	8				2		8
2				256		32	4						4
216		40			64	32	4	256	2	16			
3						32	2	512	1				
31/2					32	32							
4			Negative	64	64	32							
41/2	40	64	Negative	64		32	4	128					
5	40	64		32	128	32	4						
51/2	32	64						128			1		
6				32		1							
61/2				32									
7		64											
712		32											
8				64									
812		32											
13							1					16	
14												16	
1416												2	

* Died twentieth postoperative day following a right upper lobectomy performed on August 21, 1952.

† Died of heart failure on December 11, 1956.

Died of probable cerebral vascular accident on December 23, 1956.

§ Right upper lobectomy performed on November 11, 1954.

¶ Left apical posterior segmental resection performed on May 16, 1956.

** Right upper lobectomy performed on November 2, 1956.

†† Left apical posterior segmental resection performed on March 12, 1958.

through v. Sputum culture revealed staphylococci and pneumococci; tubercle bacilli were not found. The tuberculin and histoplasmin skin tests were both read as 4 plus.

Treatment with streptomycin and penicillin caused symptoms to subside rapidly. While in the sanatorium, cultures of sputum were made repeatedly for tubercle bacilli and fungi. No tubercle bacilli were ever found, but sputum collected in October 1951 yielded H. capsulatum. (Figs. 2A and 2B.) Thereafter this organism could be isolated regularly and easily from the sputum by several laboratories. (Table IV.) Complement fixation tests for histoplasma antibodies were first performed in November 1951. They were found to be persistently positive at a significant titer. (Table V.)

Because the cavitary lesion of the lung was localized in the right apex, the patient was referred to the University of Chicago Clinics for lobectomy. A chest roentgenogram taken shortly before the operation showed enlargement of the right apical cavity. (Fig. 1B.) A right upper lobectomy was performed on August 21, 1952. Culture of the contents of the pulmonary cavity yielded a heavy growth of H. capsulatum. (Fig. 3.) The histopathology of the removed lesion of the lung is shown in Figures 4A, 4B and 4C. The outer portion of the cavity wall was thick and fibrous, with collections of darkly staining lymphocytes, monocytes and plasma cells scattered throughout. Toward the lumen of the cavity the tissue became more granular, with caseous material on its surface. This material contained degenerating cells and

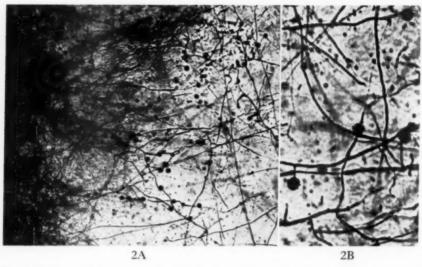


Fig. 2. Case 1. A, direct sputum culture of H. capsulatum grown on corn meal agar. Photograph is at the margin of the culture which shows the characteristic mycelia and tuberculate chlamydospores. \times 100. B, same culture under high power magnification showing identifying histoplasma spores with tuberculate borders. \times 300.

scattered macrophages filled with histoplasma organisms. The macrophages appeared to occupy the surface most adjacent to the lumen where they were continually shed to become part of the cavity content.

The postoperative course was stormy, due to the low pulmonary reserve of the patient. When recovery seemed assured, a massive hemorrhage developed from a silent peptic ulcer and the patient died on the twentieth postoperative day. At autopsy, the histoplasma infection was found confined only to the right lung. No other organs had been involved.

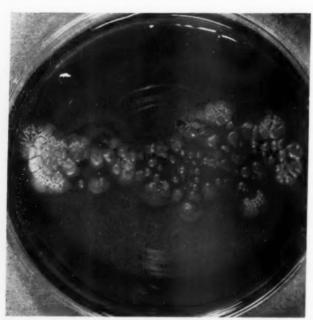


Fig. 3. Case I. Photograph of direct culture of H. capsulatum on enriched blood agar from the caseous material in the pulmonary cavity removed August 21, 1952. Note the waxy cerebriform character of the colonies.

Case II. T. M., a fifty year old white man, was admitted on June 6, 1950. He was born and lived in Macon County all of his life. (Table I.) For the past twenty-five years he had worked in a billiard parlor in Decatur. Bilateral apical pulmonary lesions were first recognized in 1949 on a chest roentgenogram taken in a mass survey. (Fig. 5A.) He denied symptoms except for chronic cough with moderate amount of sputum. There had been no loss in weight.

There was no history of tuberculosis in his immediate family. He did have contact with a sister-in-law who had been treated for tuberculosis in a sanatorium twelve years previous to his admission but she is now well. His father lives on a farm outside Decatur where the patient visited occasionally. He also cleaned a chicken house every few months on a farm he owned for some years before his hospitalization. His health generally had been good. He had had pneumonia in 1928 for which he was hospitalized. Three weeks before this admission he had an acute febrile illness and was treated with "penicillin and sulfa drugs."

On admission he weighed 141 pounds. He denied chest pain, hemoptysis, fatigue or weakness. His appetite was good. He had a cough which produced a half ounce of sputum a day. He smoked two packs of cigarettes per day. He appeared somewhat pale and undernourished. There were no lesions of the skin of mucous membranes; lymphadenopathy was not present. The chest appeared normal. There was slight dullness to percussion over the upper left side of the chest associated with bronchovesicular breathing and numerous coarse and medium rales in this area. The right side of the chest showed no abnormalities. The heart was normal. The blood pressure was 140 mm. Hg systolic and 90 mm. Hg diastolic. There were no abdominal masses. The spleen and liver were not

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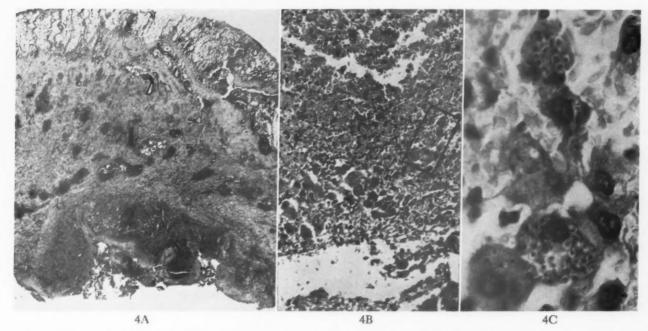


Fig. 4. Case i. A low power photomicrograph of the wall of the cavity showing the dense fibrous capsule containing collections of lymphocytes (1). Toward the lumen is a layer of granulation tissue (2). Next to the lumen is a layer of caseous material containing degenerating cells and large macrophages (3). Hematoxylin-eosin \times 10. B, highpower photomicrograph of lumen border showing necrotic debris, degenerating cells, and a band of large macrophages filled with yeast-phase histoplasma organisms. \times 250. C, oil emersion photomicrograph of area in square of Figure 4B showing the characteristic tissue phase (intracellular organisms) of H. capsulatum. \times 1300.

palpable. The diagnosis on admission was moderately advanced bilateral pulmonary tuberculosis.

The clinical and laboratory findings are shown in Tables 11 through v. The roentgenogram of the chest again showed coarse mottling in the upper third of both lung fields, similar to that noted in 1949. (Fig. 5A.) The skin tests were read as 1 plus with tuberculin, 3 plus with histoplasmin, and negative with blastomycin. By 1955 the result of the tuberculin skin test was also strongly positive (3 plus). Repeated examinations of sputum for tubercle bacilli were negative. H. capsulatum was isolated intermittently only during the first few years of observation. (Table IV.) Cultures in recent years have been impossible because of minimal raising of sputum. The complement fixation test for histoplasma antibodies has been repeatedly positive in high titer for the nine years of protracted study. (Table v.)

During these past nine years the patient has never been particularly ill. While in the sanatorium for four months he gained 35 pounds without benefit of any therapy. Since this time he has been followed up in the clinic at intervals. At present he weighs 177 pounds and has continued to work. He has a slight cough with expectoration but no dyspnea. The chest lesions have periodically shown progression and improvement. At the present time extensive fibrous infiltration persists in the upper thirds of both lungs. (Fig. 5B.) Cavities within both apices have appeared, although varying in size and location for eight years, as demon-

strated by planigrams. (Figs. 6A to 6D.) The persisting high complement fixing antibody titer indicates continued activity of the histoplasma infection.

Case III. P. B., a seventy-five year old white woman, was admitted on March 20, 1951. She had been a housewife and had lived in Macon County most of her life. (Table I.) Her symptoms began three weeks before admission and consisted of a moderately productive cough, without hemoptysis, associated with mild dyspnea. She complained of fever, anorexia, weakness, fatigue and loss of weight. She had experienced slight pleural pain in the left side of the chest for one week.

On admission, she gave a history of having had "pneumonia" in 1949 when she was ill for about three weeks. One brother died of pulmonary tuberculosis in 1897 at the age of twenty-five. One sister, who was also the mother of W. W. (Case I in this series), died in 1898 of tuberculosis. Two half sisters had tuberculosis, one having died of the disease in 1900 at the age of twenty-five. The other, still living, had tuberculous peritonitis in 1923. A son-in-law who had pulmonary tuberculosis lived at the patient's home.

On physical examination she weighed 90 pounds and appeared poorly nourished and chronically ill. There were no lesions of the skin or mucous membranes; lymphadenopathy was not present. There was an increase in the anteroposterior diameter of the chest, which was hyperresonant to percussion. The

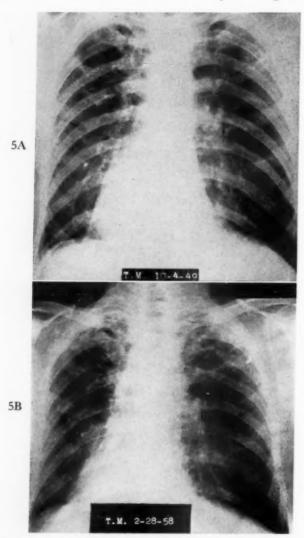


Fig. 5. Case II. A and B, chest roentgenograms taken approximately eight years and four months apart, showing essentially static appearance of bilateral apical and hilar infiltrates due to H. capsulatum.

breath sounds were amphoric in the left apex, in which numerous coarse rales were heard, and were diminished throughout the remainder of the chest. No rales were heard on the right side. The heart was not enlarged. A systolic murmur was heard on auscultation. The blood pressure was 195 mm. Hg systolic and 100 mm. Hg diastolic. A chest roentgenogram revealed marked emphysema, with pleural and apical fibrosis and cavitation on the left side. (Figs. 7A and 7B.) Calcifications were prominent in the right lung. This was diagnosed as active pulmonary tuberculosis. The clinical and laboratory findings are shown in Tables II through v. The tuberculin skin test was reported as 2 plus and the histoplasmin skin test as 3 plus. While in the sanatorium for approximately eight months, repeated examination of sputums failed to reveal tubercle bacilli. (Table IV.) Five specimens of sputum collected from November 18-24, 1951,

were found to be positive for H. capsulatum. Since this time up to 1955, all sputum specimens have been negative. The complement fixation test for histoplasma antibodies has always been negative. (Table v.)

With bedrest alone this patient gained 30 pounds while in the sanatorium. During four years of observation the x-ray picture did not change. Although the cavity persisted, the wall appeared to show increasing calcium deposition, probably compatible with healing or more effective walling off of the infectious process. (Figs. 7C and 7D.) The patient was considered to have inactive cavitary histoplasmosis in 1955.

During the next two years the patient was confined at home with arteriosclerotic heart disease. On November 29, 1956, she was admitted to the Decatur Macon County Hospital and was treated for an acute pneumonia as revealed by x-ray examination. She died on December 11, 1956, at the age of eighty from heart failure. Permission to perform an autopsy was not obtained.

CASE IV. B. C., a forty-nine year old white man, was admitted on May 28, 1951. He was born in Cook County and lived there for twenty-five years. He moved to the central region of Illinois and worked at a variety of jobs as a laborer. (Table 1.) From 1943 to 1949 he was employed as an oiler by the Denver and Rio Grande Railroad; he quit because of progressive weakness and fatigue. From 1949 to 1951, just prior to his hospital admission, he worked as a brush salesman. The onset of symptoms began in April 1949 as malaise, weakness and fatigue. A chest roentgenogram in April 1950 showed diffuse cloudiness, supposedly resulting from the inhalation of gases during the Effingham, Illinois, hospital fire, at which time a daughter-in-law was lost. A productive cough developed; occasionally the sputum was bloody. Night sweats, mild fever and gradual loss of weight began in January 1951. The first examination of sputum in May 1951 was negative for tubercle bacilli. At this time he was examined at the Barnes Hospital Clinic, St. Louis, Missouri, where a diagnosis of bilateral pulmonary tuberculosis was made. Examination of sputums again revealed no tubercle bacilli.

At the time of admission to the Macon County Tuberculosis Sanatorium, his history revealed no known cases of tuberculosis among his family, friends or associates. He had had brief contact in 1933 with a neighbor who had spent five years in a tuberculosis sanatorium, but who reportedly is now in good health. He had suffered two attacks of pneumonia at ages twelve and nineteen years. Before April 1949 there had been no history of chest pain or dyspnea, but cough, which was a prominent symptom, had yielded 2 to 3 ounces of sputum daily. He showed slight evidence of weight loss and appeared chronically ill. There were no lesions of the skin or mucous membranes. There was dullness to percussion over the left upper half of the chest bilaterally. The heart showed

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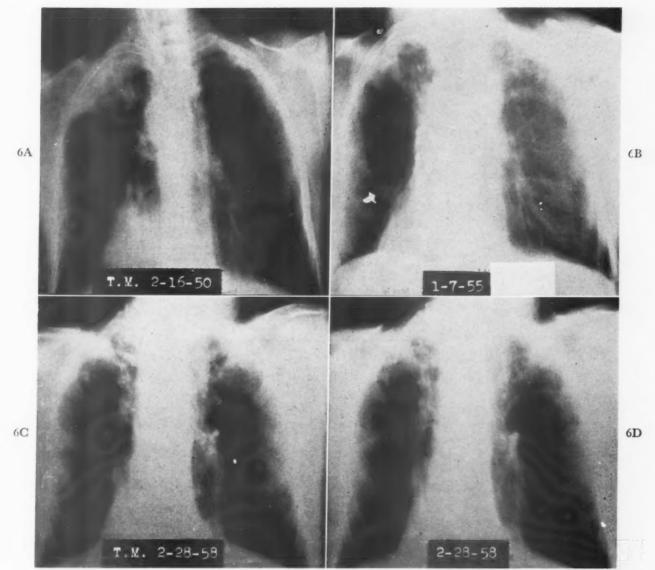


Fig. 6. Case II. A through D, planigrams taken over an eight-year period showing varying size and location of apical cavities.

no abnormalities. The blood pressure was 108 mm. Hg systolic and 80 mm. Hg diastolic. No abdominal masses were felt. Neither the spleen, liver nor kidneys was enlarged. The clinical and laboratory findings are summarized in Tables II through v. The diagnosis on admission was far advanced bilateral tuberculosis.

The roentgenogram revealed extensive bilateral apical infiltrates with a large cavity on the left. Fibrosis was present throughout both lung fields but more extensively on the left. Hilar calcification was present also. (Fig. 8A.) Skin tests were 2 plus with tuberculin, 3 plus with histoplasmin and negative with blastomycin and coccidioidin. Repeated smears and cultures of sputum were negative for tubercle bacilli. (Table IV.) Cultures of sputum for H. capsulatum have been repeatedly positive without exception, and the organism can easily be obtained in pure culture

at any time up to the present. Repeated complement fixation tests for histoplasma antibodies have been invariably positive for over eight years. (Table v.)

In spite of negative cultures for tubercle bacilli, the patient was given a five-month course of antituber-culous therapy consisting of streptomycin and PAS. The patient gained 7 pounds in weight and the sputum decreased in amount. In spite of apparent clinical improvement with bedrest and chemotherapy, the lesions in the lungs progressed. Several episodes of massive hemoptysis occurred in December 1956. Extensive bilateral infiltration and cavitation has ensued. (Figs. 8B to 8D.)

This patient returned to his work as a brush salesman for two years, but then found that he was unable to continue this job because of dyspnea, mild fever, severe cough, and copious expectoration up to 300 ml. daily. During 1957 he took a light job as a janitor,

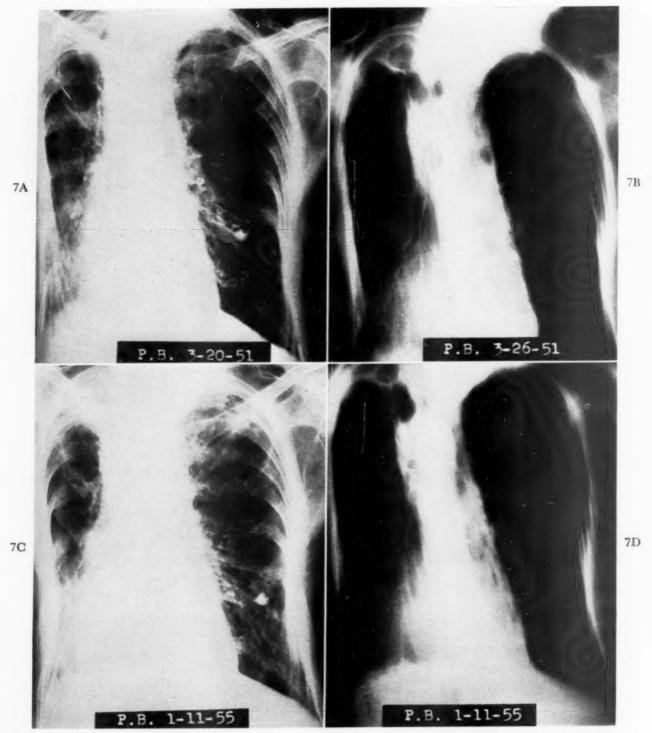


Fig. 7. Case III. A through D, chest roentgenograms taken approximately four years apart showing the static appearance of the left apical lesion with cavity. Note the thin rim of calcium deposit lining the cavity and calcification in the right lung field.

working five hours per day. On his last examination in January 1958 his weight was 114 pounds. His vital capacity was 1.3 L. or 68 per cent of normal. He appeared emaciated and chronically ill. Chest examination revealed dullness to percussion over both apices with amphoric breath sounds. Loud expiratory

wheezes on the right and moist rales in the middle thirds bilaterally were present. There was no evidence of extrapulmonary histoplasmosis. Tubercle bacilli were not isolated whereas H. capsulatum has again been easily isolated recently from a freshly collected sputum specimen.

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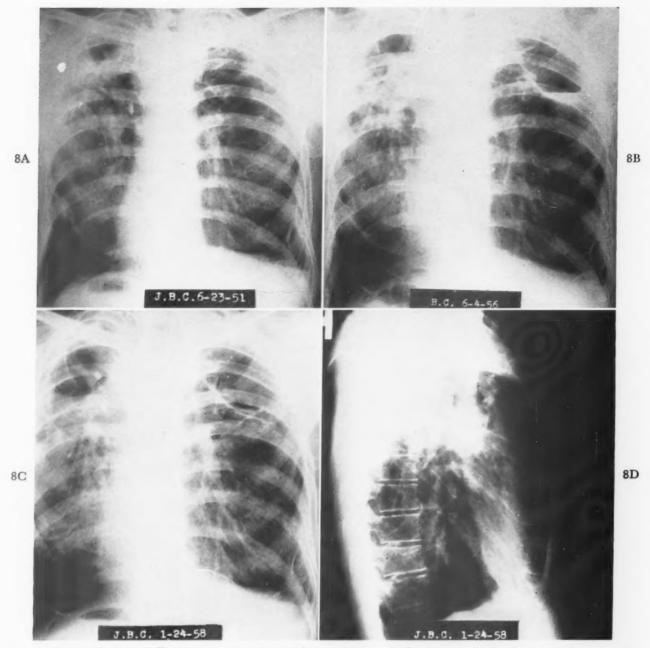


Fig. 8. Case iv. A through D, chest roentgenograms taken approximately five years apart showing marked progression bilateral infiltration and enlargement of the cavities. Left hilar calcification is present. Chest roentgenograms taken January 24, 1958, show greater extension of the pulmonary histoplasmosis and large cavity formation.

Case v. H. D., a sixty-two year old white man, was admitted on January 11, 1955. He was born in Tippecanoe County, Indiana, but had lived in Macon County for thirty-six years where he worked as a locomotive engineer for the Wabash Railroad. (Table I.) A chest lesion was first discovered in a mass survey program for tuberculosis in the summer of 1951. He was referred to the Clinic of Macon County Tuberculosis Sanatorium for follow-up on November 10, 1951. History revealed that there had been a single slight contact with a tuberculosis infection in his

sister-in-law. There were no known cases of tuberculosis in his family. He had never lived on a farm although he had raised pigeons in 1935. His symptoms consisted of cough, productive of a small amount of sputum. There had been no hemoptysis, chest pain, malaise or fatigue. Slight anorexia had developed, and he had lost 10 pounds in weight during the previous six months. He weighed 144 pounds. The chest roentgenogram showed an infiltrative lesion in the upper lobe of the right lung. (Fig. 9A.) The left mid-lung field showed a small area of infiltration.

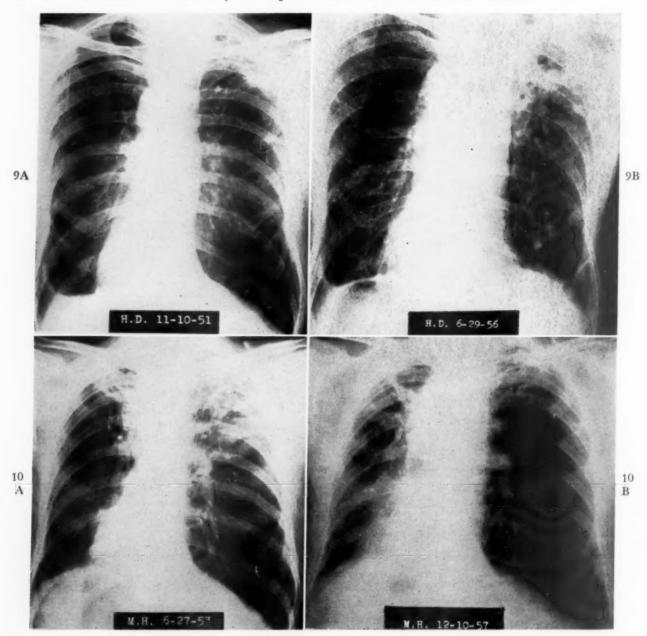


Fig. 9. Case v. A and B, chest roentgenograms taken approximately four years and seven months apart showing enlargement of the right apical lesion and increase in size of the cavity.

Fig. 10. Case vi. A and B, chest roentgenograms taken approximately four years and six months apart, showing persistence of the bilateral apical lesions.

Three sputum cultures for tubercle bacilli were negative. The tuberculin skin test was read as negative and the histoplasmin skin test as 3 plus.

The patient was seen again at the clinic in November 1953. The chest lesions remained essentially the same. Cough, productive of a large amount of sputum, and fatigue were the predominant symptoms. The tuberculin skin test again was read as negative and the histoplasmin skin test as positive. A complement fixation test showed a high titer (1:64) for histoplasma antibodies. Cultures of sputum for tubercle bacilli were again negative. H. capsulatum was

readily cultured from the sputum on the initial attempt.

In November 1954, hospitalization was recommended. On admission to the sanatorium he weighed 123 pounds. His chief symptom still was a chronic productive cough. The sputum had never been foul. Some dyspnea had developed in the past year, but there had been no chest pain, associated chills, fever or night sweats. Fatigue and weakness had occurred during the past three years. A Parkinsonian tremor had also developed over the past eight years which forced him to retire in 1948.

The patient appeared to be well developed but undernourished and chronically ill. Marked tremor was present. There were no lesions of the skin and mucous membranes, nor was lymphadenopathy present. The chest showed lack of expansion on the right side. There was dullness to percussion over the right apex where bronchovesicular breath sounds and rales were heard. The heart showed no abnormalities. The blood pressure was 130 mm. Hg systolic and 80 mm. Hg diastolic. There were no abdominal masses, and the liver and spleen were not enlarged. The clinical and laboratory findings are shown in Tables 11 through v. The repeated skin tests were positive with histoplasmin but negative with tuberculin. Cultures of sputum for tubercle bacilli were negative, but always positive for histoplasma organisms. (Table IV.) The complement fixation test for antibodies to H. capsulatum was again positive in a significantly high titer of 1:64. (Table v.) A diagnosis of chronic active pulmonary histoplasmosis was made.

During seven months of ambulatory care and treatment with INH in the sanatorium, the patient gained 17 pounds. Histoplasma organisms had been isolated repeatedly from his sputum (Table IV) and the complement fixation test had remained positive. Tubercle bacilli had never been isolated. During five and a half years of observation there had been a gradual progression of the right apical lesion with enlargement of the cavity and increasing fibrosis in the remainder of the right lung. (Fig. 9B.) When last seen at the clinic on June 29, 1956, the patient appeared weaker and his Parkinson's disease was more marked. His cough had continued, but there was no evidence of extrapulmonary histoplasmosis. On December 21, 1956, an acute irrational episode developed and the patient was admitted two days later to the Wabash Railroad Employees Hospital where a diagnosis of pneumonia was made. He died a few hours later. History revealed that there had been no febrile symptoms or change in the character of sputum before his sudden illness. Permission to perform a postmortem examination was not obtained, but it is unlikely that death was due to an acute pneumonic process.

CASE VI. M. H., a seventy year old white man, was admitted on August 23, 1953. He was referred to the Sanatorium Clinic on June 27, 1953, for routine examination by his physician because of a cold, and a pulmonary lesion was incidentally discovered on a roentgenogram.

The patient was born in Fayette County and was a farmer all his life. (Table 1.) He had been retired for five years but visited the farm frequently. His mother had died of tuberculosis at the age of seventy-five and one sister was treated in the sanatorium for tuberculosis. He had generally been well but had "left-sided" pneumonia at age thirty. He had not

been feeling well beginning in 1950 and since that time had gradually lost weight. Cough with expectoration of blood-streaked sputum had persisted for the past three years. He had experienced slight dyspnea with associated fatigue for a year. In July 1953 he had an episode of pain in the left side of the chest. For a few months before admission he had had night sweats.

On admission he weighed 119 pounds, whereas one year previously he had weighed 133 pounds. He appeared well developed, although undernourished and chronically ill. There were no lesions of the skin or mucous membranes. There was dullness to percussion over the upper left side of the chest and rales were heard in the upper right side of the chest. The hear was normal. The blood pressure was 134 mm. Hg systolic and 80 mm. Hg diastolic. There was no lymphadenopathy. The liver and spleen were not enlarged; no abdominal masses were felt.

The clinical and laboratory findings are shown in Tables II through v. The chest roentgenogram showed bilateral apical pulmonary infiltrates with cavitation. (Fig. 10A.) Skin tests with tuberculin and histoplasmin were both positive, 3 plus with the latter antigen. The diagnosis on admission was bilateral far-advanced pulmonary tuberculosis. However, repeated sputum cultures for tubercle bacilli were negative, whereas H. capsulatum has been easily isolated from the sputum during the past five years. (Table IV.) Eight of ninety-seven sputum smears for tubercle bacilli were read as positive, although cultures were never positive. Guinea pig inoculation also failed to produce either a positive tuberculin test or tuberculous lesions in the animals. The complement fixation test for histoplasma antibodies has been consistently present in significant titer for five years. (Table v.)

The patient was in the sanatorium for sixteen months; he gained 40 pounds during this time. He was treated with complete bedrest for five months and with streptomycin, PAS and INH until November 1954. He was last seen in the Sanatorium Clinic in June 1958, at which time he was quite symptom-free except for a slight cough with expectoration. His weight had remained constant at 155 pounds. A chest roentgenogram taken in December 1957 showed persistence of the fibrous apical lesions bilaterally with cavitation on the left. (Fig. 10B.) The complement fixation test at present remains positive at a titer of 1:32, indicating continued activity of his histoplasma infection.

Case VII. C. B., a forty-seven year old white man, was admitted on November 9, 1953. A lesion of the lung was discovered in August 1953 on a roentgenogram taken in a mass survey for tuberculosis. He had lived in Macon County for thirty years and was employed as a yard clerk for the Illinois Central Railroad. (Table I.)

He had first been referred to the Sanatorium Clinic as early as January 1944. At that time he stated that

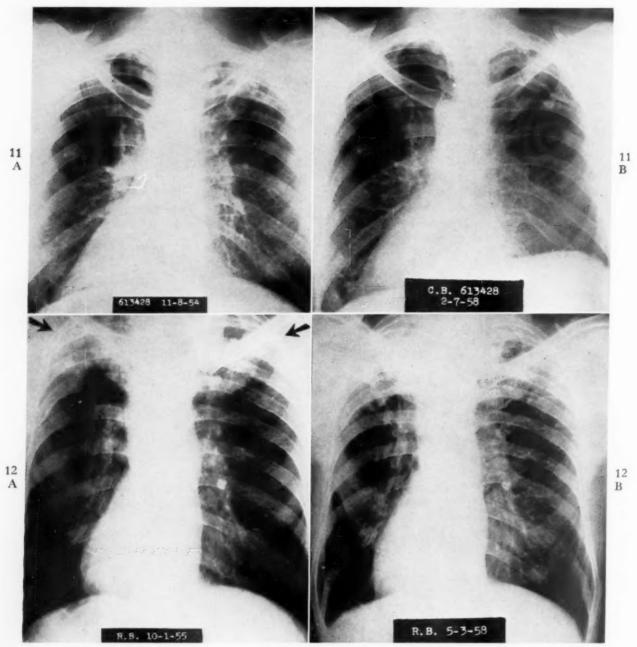


Fig. 11. Case vii. Chest roentgenograms. A, before right upper lobectomy showing infiltrative lesion with multiple small cavities. B, three years and three months postoperatively. There is no recurrence of the lesion.

FIG. 12. Case VIII. A and B, chest roentgenograms taken at an approximate interval of two years and seven months showing enlargement of a cavity in the left apical infiltration with no change in fibrous scarring on the right.

his three sisters, two brothers, father and stepmother had all died of tuberculosis, the last death occurring in 1930. He also stated that he had had influenza in 1917, pneumonia in 1943 and an acute febrile illness in 1944. A chest roentgenogram taken in 1944 was said to be normal.

When the lesion of the lung was first discovered in the survey of August, the patient was referred again to the Sanatorium Clinic in September 1953. He then gave a history of cough with non-foul sputum, fatigue, exertional dyspnea, malaise and anorexia. There had been a 25 pound loss in weight. Night sweats and fever were not present. Chest pain had been experienced for eight days before admission. He had felt poorly since contracting a "cold" in December 1952.

On admission he weighed 159 pounds. He appeared to be well developed and well nourished, and certainly not chronically ill. There were no lesions of the skin or mucous membranes. The chest showed no abnormalities; no rales were heard. The blood pressure was 110 mm. Hg systolic and 70 mm. Hg diastolic. There were no abdominal masses. The liver, spleen and lymph nodes were not enlarged.

The clinical and laboratory findings are shown in Tables II through v. Skin tests with tuberculin and histoplasmin were both positive. The roentgenogram of the chest revealed a right apical infiltration with cavitation confirmed by planigram. (Fig. 11A.) The left lung showed some emphysema and calcification in the middle third. The diagnosis on admission was far advanced active cavitary tuberculosis.

The patient remained in the hospital for fourteen months during which time he was on a regimen of complete bedrest for five months and was treated with streptomycin, PAS and INH because of the pronounced family history of tuberculosis. He gained 47 pounds in weight and the right apical infiltrate appeared to clear slightly.

During his hospital stay repeated examinations of the sputum were negative for tubercle bacilli. (Table IV.) H. capsulatum, however, was cultured on several occasions from the sputum. Complement fixation tests for histoplasma antibodies were persistently positive in significant titer. (Table V.) The diagnosis was consequently changed to chronic cavitary histoplasmosis. Since the cavitary lesion was unilateral and well localized, surgical removal was advised. An upper right lobectomy was performed by Dr. William Adams at the University of Chicago Clinics on November 11, 1954. H. capsulatum was cultured from caseous material within the lumen of the cavity as well as from a ground tissue suspension of the cavity wall.

The postoperative course was uneventful, although injury to the right phrenic nerve resulted in prolonged paralysis of the right diaphragm. At present, virtually normal mobility of the right diaphragm has been restored. There has been no further cough. The sputum has remained negative for histoplasma organisms and the complement fixation titer of histoplasma antibodies has slowly fallen over the threeand-a-half year period since surgery, although still persisting at a low titer. The patient has been back to full employment for the past two and a half years. Slight fatigue and dyspnea on exertion persists. His vital capacity shows approximately 32 per cent reduction from the normal. His weight is now 194 pounds. There has been no roentgenographic evidence of recurrence of the chest lesion some three years following surgical resection. (Fig. 11B.)

Case VIII. R. B., a sixty-seven year old white man, was admitted on June 20, 1955. This retired freight and passenger conductor worked as a railroad employee from fifteen years of age to retirement in August 1952. He retired to the country where he raised chickens for some time and cleaned the foul and dusty coops but once a year. He was born in

Fayette County, in which he lived all his life. (Table 1.) He has had no known major illness. His only contact with tuberculosis was a friend who is now hospitalized in a sanatorium in Normal, Illinois.

The patient first became aware of his chest disease in November 1952, as a result of a routine roentgenogram taken by the railroad company. The sputum at that time was examined for tubercle bacilli, but none were found. A diagnosis of inactive tuberculosis was made. The next roentgenogram was taken in 1955 during a mass survey. Following this, he was sent to the Macon County Tuberculosis Sanatorium for further study.

On admission, his chief symptom was a four-month old cough productive of 2 ounces of purulent sputum per day. In March 1955 he had hemoptysis of about 1 pint of blood over a three-day period. There had been no history of fever, sweats, chills, fatigue or weakness. During the preceding year he had lost 14 pounds, but his appetite had always been poor. He denied any susceptibility to respiratory infections.

On physical examination he appeared thin but well nourished and neither acutely nor chronically ill. He weighed 126 pounds. The skin and mucous membranes showed no lesions and there was no lymphadenopathy. The heart revealed no abnormalities. The blood pressure was 140 mm. Hg systolic and 80 mm. Hg diastolic. The chest was symmetrical. The percussion note was slightly diminished on both sides; the breath sounds were bronchovesicular and rales were heard bilaterally. The abdomen was soft and not tender. The liver, spleen and kidneys were not palpable. Tuberculosis was considered to be the diagnosis, but histoplasmosis was also suspected.

The clinical and laboratory findings are shown in Tables II through v. The roentgenogram of the lung showed infiltrations in the apices bilaterally, with cavitation on the left. (Fig. 12A.) Skin tests with tuberculin and histoplasmin were both positive. Repeated examinations of sputum for tubercle bacilli were negative. (Table IV.) On the other hand, H. capsulatum was easily cultured from the sputum by several different laboratories. The complement fixation test for antibodies to the histoplasma organism was positive in a serum dilution of 1:256.

The patient remained in the sanatorium for three months, during which time he gained 7 pounds. He received no drug therapy. His physical state has apparently remained quite static. When last seen in May 1958, he had a slight cough, fatigue and exertional dyspnea, but felt generally well otherwise. He weighed 127 pounds. He denied having night sweats, fever or chest pain. Physical examination revealed bronchovesicular breath sounds in the left apex with post-tussive rales. The cavitary lesion on the left had persisted and appeared to be slightly larger and more discrete, with increased infiltration. (Fig. 12B.) The complement fixation test has remained strongly positive, indicating continued activity of pulmonary histo-

plasmosis. The patient has refused surgical resection of the cavitary lesion.

CASE IX. R. M., a fifty-eight year old white man, was admitted on September 26, 1955. His pulmonary lesion was first discovered by routine roentgenographic examination in July 1955. The patient was born in Douglas County and lived in central Illinois all his life. He had worked as a pipe fitter for a gas company for the past ten years. (Table 1.) There was no history of any tuberculosis contacts. A chest roentgenogram taken in 1944 was said to be negative. He was referred to the sanatorium as a case of moderately advanced tuberculosis. On admission he stated he felt well. He had a mild cough and raised some sputum in the morning, but he had never experienced hemoptysis. There was no history of fever, dyspnea, fatigue, night sweats or anorexia. He had lost about 12 pounds of weight during the previous year.

On physical examination he weighed 133 pounds and did not appear acutely or chronically ill. There were no lesions of the skin or mucous membranes. The chest expanded equally. Rales were heard in the left apex. The heart was normal and the blood pressure was 152 mm. Hg systolic and 90 mm. Hg diastolic. There was no lymphadenopathy; the liver and

spleen were not enlarged.

The clinical and laboratory findings are shown in Tables II through v. The chest roentgenogram showed calcification and dense infiltration with cavitation in the left apex. (Fig. 13A.) Skin tests with tuberculin and histoplasmin were positive. (Table IV.) Only four of eighteen sputum smears showed acid-fast organisms, while all cultures of sputum for tubercle bacilli were negative. However, cultures for H. capsulatum were repeatedly positive. The initial complement fixation test was positive for histoplasmosis at a titer of 1:128. (Table v.)

While in the sanatorium, the patient gained weight and continued to be asymptomatic. Because of localization of the histoplasma lesion to the left apex, surgical resection was advised. On May 16, 1956, a left apical posterior segmental resection was performed at the University of Chicago Clinics. Postoperative recovery was uneventful. A roentgenogram of the chest twenty-two months after operation showed slight scarring in the region of the resection. Cultures of the cavity wall were positive for H. capsulatum and negative for tubercle bacilli. After surgical removal of the cavity the sputum became negative for histoplasma organisms and has remained so. The complement fixation test has fallen to very low titers, indicating that surgical removal of the focus of infection has been achieved. When last seen in March 1958, the patient was asymptomatic and working regularly. His weight was 138 pounds. The chest roentgenogram remained unchanged and continued to show only the slight scarring at the site of the resection. (Fig. 13B.)

CASE X. C. W., a fifty-two year old white man, was admitted on October 29, 1955. He was born in Pana, Illinois, where he lived until the age of fourteen. Since then he has lived in Macon County where he has been employed as a printer all his working life, except for one year when he worked for the railroad and another year when he worked as a farmer. The only history of tuberculosis in the family has involved his mother-in-law. She has had tuberculosis of the hip, which is now inactive.

Frequent chest microfilms from 1949 through 1954 had been reported normal. A chest lesion was first detected on a roentgenogram taken during a mass survey for tuberculosis at Decatur, Illinois, in the summer of 1955. At that time he had only mild fatigue but was otherwise completely asymptomatic. In particular, there was no chest pain, loss of weight,

anorexia, cough or expectoration.

On admission, he appeared well developed, well nourished and not chronically ill. His weight was 139 pounds. There were no lesions of the skin or mucous membranes; lymphadenopathy was not present. The chest was symmetrical. The percussion note was diminished over the left apex, associated with bronchovesicular breath sounds and a few rales in the area. The heart examination revealed no abnormalities. The blood pressure was 130 mm. Hg systolic and 80 mm. Hg diastolic. The abdomen was soft and a scar in the right upper quadrant was visible, the result of a subtotal gastrectomy performed in March 1951 for adenocarcinoma of intermediate grade malignancy. The liver and spleen were not enlarged.

The clinical and laboratory findings are shown in Tables II through v. The chest roentgenogram revealed an infiltrative lesion with cavitation in the left apex. (Fig. 14A.) On admission, tuberculosis was suspected. The skin test with tuberculin was mildly positive but strongly positive with histoplasmin. Repeated examination of sputum for tubercle bacilli by smear and culture revealed no organisms. (Table IV.) On the other hand, cultures of sputum for H. capsulatum were repeatedly positive. The complement fixation test for histoplasma antibodies was positive at a

high titer of 1:256. (Table v.)

The patient was treated with bedrest in the sanatorium for a month but on November 28, 1955, he left against medical advice. He has been working steadily in his print shop ever since and participates in bowling regularly. He has had no symptoms except for a slight productive cough. His weight has remained constant since 1955. A chest roentgenogram, taken in February 1957, showed left apical clearing, although the cavity has become more discrete. Sputum cultures were negative for H. capsulatum at that time. His most recent roentgenogram showed the well circumscribed cavity persisting in the left apex. (Fig. 14B.) The complement fixation test fell in titer as apical clearing occurred. However, the persisting lower but positive

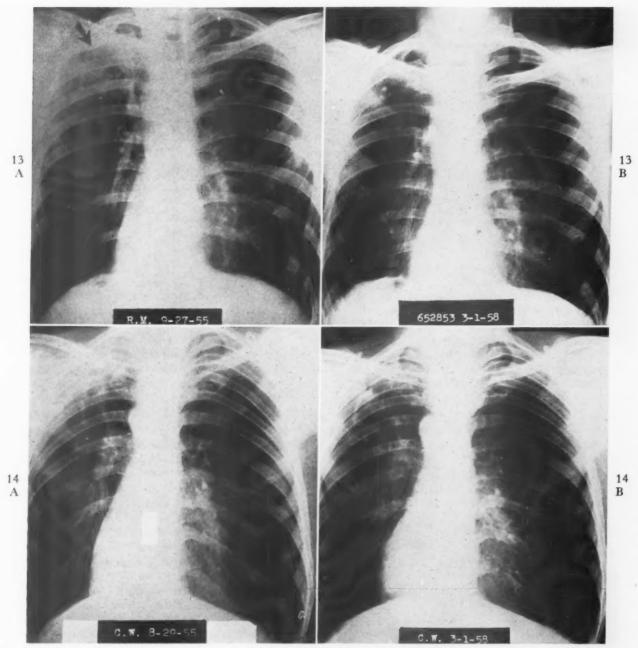


Fig. 13. Case IX. Chest roentgenograms; A, approximately eight months before left apical posterior segmental resection showing character of left cavitary lesion. B, twenty-two months after operation. There is no recurrence of the lesion; slight scarring is noted at the site of resection.

Fig. 14. Case x. A and B, chest roentgenograms taken at a two and a half year interval showing increasing discreteness of the left upper lobe cavitation but with some clearing of the infiltrate.

titer would indicate continuing activity of the disease process within the more effectively walled-off cavity.

CASE XI. R. D., a forty-eight year old white man, was admitted on May 20, 1956. He was born in Coles County, located in central Illinois, where he lived essentially all his life, working as a gardener specializing in tree planting and care. (Table I.) He had been to California on several occasions. The last trip was

during February and March 1956 at which time he became easily fatigued. He worked at an outdoor job in the San Joaquin Valley during that time. The only contact with tuberculosis was through a brother who died of this disease in 1929. He was referred to the sanatorium by a physician who discovered pulmonary lesions by roentgenographic examination on May 1, 1956.

At the time of admission the patient stated that he

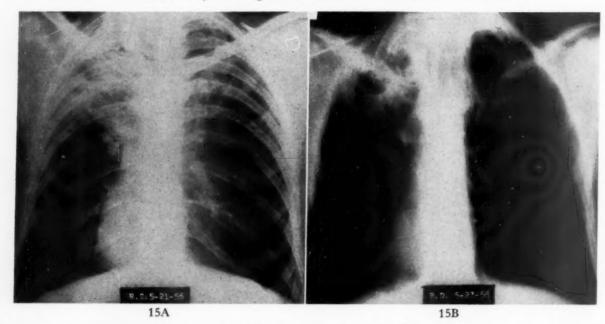


Fig. 15. Case xi. Chest roentgenograms. A, regular anteroposterior. B, planigram showing large infiltrative lesion in the left upper lobe containing multilocular cavities.

had not felt well since the summer of 1955 when he first noticed fatigue. During the past year he had lost 8 pounds in weight. Through February and March 1956 fatigue became pronounced, and in April he had a febrile episode described as "flu." The symptoms were cough productive of sputum, fever, night sweats and pain in the left side of the chest. There was no hemoptysis. He saw no physician at this time. His diagnosis on admission to the sanatorium was far advanced bilateral tuberculosis.

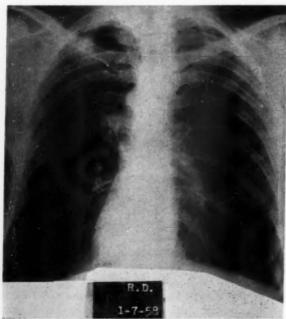


Fig. 16. Same case. Chest roentgenogram taken January 7, 1958, showing healed left apical lesion with residual linear scarring.

His weight was 117 pounds, as compared to 125 pounds one year previously. He appeared chronically ill. There were no lesions of the skin or mucous membranes. Chest expansion was equal bilaterally. There was dullness to percussion and post-tussive rales were heard anteriorly and posteriorly over the upper left lung field. The heart was normal and the blood pressure was 112 mm. Hg systolic and 78 mm. Hg diastolic. There was no lymphadenopathy, and the liver and spleen were not enlarged.

The clinical and laboratory findings are shown in Tables II through v. The chest roentgenogram showed bilateral apical infiltration, although more extensive on the left. (Fig. 15A.) A planigram revealed a loculated cavity in the left apex. (Fig. 15B.) Skin tests with tuberculin and histoplasmin were positive. A coccidioidin skin test was negative. Sputum smears and cultures for tubercle bacilli were repeatedly negative. Five cultures over a two-month period were positive for H. capsulatum. (Table IV.) The complement fixation test for histoplasma antibodies was positive in a serum dilution of 1:16. (Table v.) No complement fixing antibodies to coccidioidin have been present in the serum.

After being admitted to the sanatorium, the patient was started on antituberculous therapy consisting of streptomycin and INH. However, he left the sanatorium against medical advice after a short stay. He moved to California in January 1957 and returned to Coles County, Illinois, four months later. He had received no treatment or examination until he was seen again in the Sanatorium Clinic on January 7, 1958. His only complaints were slight cough productive of sputum and mild dyspnea. His weight was 129½ pounds, although he had weighed as much as

136 pounds after leaving the sanatorium in 1956. His alcoholic intake had been notable, however.

The chest roentgenogram taken in January 1958 (Fig. 16) showed a striking change. Only light fibrous infiltration remained in the right apex; the left apex showed only linear scarring. There was complete disappearance of the extensive cavitation and infiltration present previously. His complement fixation titer had fallen to 1:2, compatible with healing of the chest lesion.

CASE XII. E. C., a fifty-eight year old white man, was admitted on September 19, 1956. Except for brief periods (months) of living in Arizona, Texas and Missouri in 1927 for health reasons, he had remained entirely in Fayette, Christian and Macon Counties, Illinois. (Table 1.)

The patient was first seen in the Sanatorium Clinic in June 1943 at which time the tuberculin skin test was positive, and the chest roentgenogram was interpreted as showing moderately advanced cavitary tuberculosis. Although he denied exposure to any one with this disease, he gave a history of hemoptysis and pleurisy during 1927. In November 1927, at the age of twenty-nine, he had suffered a severe pulmonary hemorrhage while husking corn. He continued to cough and feel weak, and had blood-streaked sputum again in 1934 and 1936. Following an episode of pleural pain, cough and expectoration in 1940, a roentgenogram was taken by his physician and the diagnosis of tuberculosis was entertained. He rested at home for three months during which time he gained weight. Upon returning to work he lost weight and continued to have right pleural pain.

On June 30, 1943, he was initially admitted to the sanatorium but left against advice on September 20, 1943. During this admission sputum cultures for tubercle bacilli and fungi were negative. Pneumothorax treatment was started but was discontinued because of extensive adhesions. A roentgenogram of the chest revealed dense fibrotic infiltration with cavitation in the upper lobe of the right lung. (Figs. 17A and 17B.) Because of repeated hemoptysis, he finally consented to enter the sanatorium for a detailed examination.

Upon admission on September 19, 1956, history revealed that he had worked as a janitor and laborer for the past five years. He had had three episodes of severe hemoptysis on September 3, 4 and 5 and again on the day before admission. He complained of some fatigue at the end of the day. There were no night sweats or fever.

The physical examination revealed a well developed, well nourished man who did not appear ill. He weighed 179 pounds. There were no lesions of the skin or mucous membranes. The chest showed diminished percussion over the right apex, and amphoric breath sounds were heard in the upper third of the right side of the chest. The heart rate

was 92. The blood pressure was 134 mm. Hg systolic and 72 mm. Hg diastolic. There was no local or generalized lymphadenopathy. The liver and spleen were not palpable.

The clinical and laboratory findings are shown in Tables II through v. The tuberculin and histoplasmin skin tests were positive. The sputum cultures were negative for tubercle bacilli but positive for histoplasma organisms. (Table IV.) The complement fixation test for histoplasma antibodies was positive in serum dilutions of 1:16. (Table v.) Compared with previous roentgenograms, there was a small increase in the size of the cavity in the apex of the right lung. (Figs. 18A and 18B.) A diagnosis of pulmonary histoplasmosis with cavitation was made. Because of the repeated hemoptysis, an upper right lobectomy was recommended.

The patient entered the University of Chicago Clinics on October 28, 1956. Cultures of the sputum were again negative for tubercle bacilli but positive for H. capsulatum. Skin tests were positive with histoplasmin and tuberculin but negative with blastomycin and coccidioidin. The blood findings were similar to those of the sanatorium admission shown in Table III. On November 2, 1956, an upper right lobectomy was performed. The patient made a good recovery, except for residual paralysis of the right diaphragm. Repeated cultures of the sputum were negative for tubercle bacilli and H. capsulatum following removal of the lesion. Cultures of the contents and wall of the cavity were positive for H. capsulatum but negative for tubercle bacilli.

One year after surgical resection this patient continued to have considerable reduction in pulmonary function and was unable to work. Further follow-up has been extremely difficult. The complement fixation test continues to be positive but has fallen gradually in titer. The last chest roentgenograms, taken in November 1957, showed no evidence of the cavitary lesion. There was fibrous infiltration and thickening of the pleura in the right apex. Paralysis of the right diaphragm was present.

CASE XIII. P. E., a fifty year old white man, was admitted on November 16, 1956. He was born and has lived all his life in Piatt County located in central Illinois. (Table I.) His only occupation had been that of a farmer, raising chickens along with livestock and grain. He gave no history of exposure to tuberculosis, although he drank raw milk from his cows. Biannual chest roentgenograms had been obtained in mass surveys for tuberculosis by this patient since 1948. These had been reported as normal until June 1956 when a pulmonary infiltrate was detected. A repeat chest roentgenogram in October 1956, again demonstrated a left apical infiltrate. Several sputum examinations for tubercle bacilli were negative. He was referred to the sanatorium for admittance.

On admission, the patient was completely asympto-

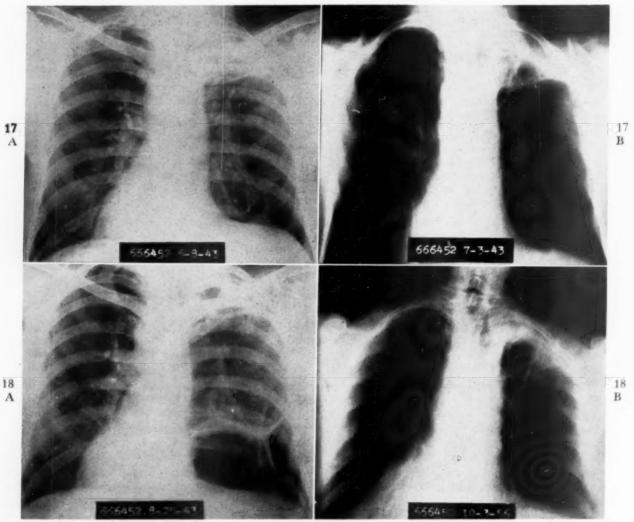


Fig. 17. Case XII. Chest roentgenograms. A, regular anteroposterior. B, planigram showing cavitary lesion in right upper lobe.

Fig. 18. Same case. Chest roentgenograms. A, regular anteroposterior. B, planigram taken approximately thirteen years later showing enlargement of the cavity, but essentially no total change in the character of the right apical lesion.

matic except for a slight productive cough. He denied fever, sweats, dyspnea, fatigue or chest pain. His weight was 182 pounds, as it had been for the past ten years. The diagnosis on admission was minimal active pulmonary tuberculosis, although histoplasmosis was seriously considered.

Physical examination revealed a healthy white man. There were no lesions of the skin or mucous membranes. The lung fields were clear. The heart was normal. The blood pressure was 128 mm. Hg systolic and 70 mm. Hg diastolic. There was no enlargement of lymph nodes, liver or spleen.

The clinical and laboratory findings are shown in Tables II through v. A chest roentgenogram showed an infiltration in the left apex without cavitation. (Figs. 19A and 19B.) The histoplasmin and tuberculin skin tests were positive. Repeated attempts to demonstrate tubercle bacilli in the sputum were unsuccessful. (Table IV.) H. capsulatum, however,

was isolated readily. The complement fixation test was positive for antibodies to H. capsulatum at a 1:2 serum dilution. (Table v.) The patient was observed for fifty-eight days in the sanatorium; he was treated with bedrest as well as antituberculous therapy consisting of streptomycin, PAS and INH. On January 12, 1957, he was discharged with a diagnosis of active histoplasmosis.

He performed his usual farming activities in a routine manner throughout the summer of 1957. He felt well and was completely asymptomatic. Frequent roentgenograms showed the left apical infiltrate to be unchanged, until the fall of 1957 when cavitation frankly occurred and increased in size. (Fig. 20.)

The patient was admitted to the University of Chicago Clinics on February 26, 1958, for surgical resection of the cavitary histoplasma infection. Intravenous amphotericin B was administered for eight days before surgery, the dosage being increased to

AMERICAN JOURNAL OF MEDICINE

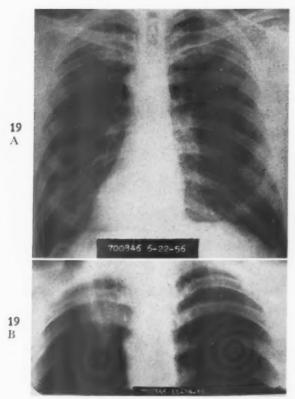


Fig. 19. Case XIII. Chest roentgenograms. A, regular anteroposterior (B), planigram five months later showing left apical infiltrate without cavitation.

80 mg. per day. The administration of benadryl and salicylates helped to keep toxic manifestations adequately repressed. It is remarkable that daily sputum cultures which had been strongly positive for H. capsulatum became absolutely sterile several days after therapy with amphotericin B* had been instituted. On March 12, 1958, a resection of the left apical posterior segment was performed by Dr. William Adams. The use of amphotericin B had to be discontinued postoperatively because of fever and shaking chills. A pneumothorax and pleural effusion necessitating repeated thoracenteses complicated the recovery period. However, the patient was discharged on the seventeenth postoperative day. Cultures of the caseous material within the cavity grew out only a few slow-growing rather atypical colonies of H. capsulatum. Repeated sputum cultures for fungi and tubercle bacilli were negative following surgery.

The patient has resumed his normal farm chores and feels very well. A recent chest roentgenogram showed complete resorption of the pneumothorax and effusion and re-expansion of the left lung. The complement fixation test for histoplasma antibodies has remained unchanged at a low titer of 1:4.

* Supplied under the trade name Fungizone® through the courtesy of E. R. Squibb & Co.

Fig. 20. Same case. Chest roentgenogram fifteen months later showing discrete left apical cavitation.

ANALYSIS OF CASES

Findings on Admission. All thirteen patients were white and more than forty-five years of age when they first came under observation. (Table 1.) Their ages ranged from forty-seven through seventy-five. Twelve were male and one was female. Their past or present occupations neither appeared to play a particular part in their illness nor pointed to a specific diagnosis. However, five patients had engaged in farming or gardening activities. All but one were thought initially to have pulmonary tuberculosis. Seven were brought to medical attention through mass surveys for tuberculosis. Two were referred by Tuberculosis Boards, and four were referred by their private physicians. All thirteen patients were born, lived and worked in central Illinois most of their lives. Central Illinois is located in the geographic area of the United States in which histoplasmin sensitivity is high. A previous study by Beadenkopf et al. has shown that over 75 per cent of high school students in Macon County, Illinois, reacted in a positive manner to histoplasmin skin test antigen [40].

A list of symptoms at the time of admission to the sanatorium is shown in Table II. Subjective findings, such as fever, sweating, chills, fatigue and malaise, usually associated with a pulmonary infectious process, were not remarkable in these thirteen cases. Four patients (Cases II, IX, X and xiii) were, in fact, considered to be asymptomatic. Cough, productive of variable quantities of sputum, was present in all patients. The sputum was purulent in five cases. Only two had frank hemoptysis while three others had blood-streaked sputum on occasion. Foul-smelling sputum, characteristic of putrid abscesses of the lung, was not characteristically present. Progressive debilitating symptomatology was not the rule, occurring in only three persons

(Cases I, IV and V).

Physical examination and history, as shown in Table III, revealed varying degrees of weight loss, ranging from 0 to 25 pounds. Symptoms compatible with the final diagnosis of histoplasmosis had been present for variable periods, ranging from one month to as long as sixteen years, before the patients were seen at the sanatorium. In all but three cases there was a history of contact with tuberculous individuals. Multiple exposures were notable in three cases. None of the thirteen patients had evidence of systemic involvement. Lymphadenopathy and hepatosplenomegaly were not present. The red blood cell counts and hemoglobin determinations were generally normal; only one patient (Case VIII) was somewhat anemic. The red blood cell sedimentation rate was moderately elevated in all but two cases. The white blood cell counts were usually normal or only slightly elevated. The urine examinations were within normal limits in all cases. Chest roentgenograms showed varying degrees of unilateral or bilateral pulmonary infiltration and cavitation which simulated tuberculosis. Hilar and/or peripheral calcifications were noted in all cases.

It is shown in Table IV that the skin tests with tuberculin were positive in all but one case. However, examinations of the sputum for tubercle bacilli were repeatedly negative, except for occasionally positive smears in two cases. In none was the sputum positive for tubercle bacilli

by culture or guinea pig inoculation.

Table IV also shows that all thirteen patients reacted in a positive manner to the histoplasmin skin test (100 per cent). Sputum examinations by direct culture or mouse inoculation were repeatedly positive for H. capsulatum in all cases. The complement fixation test for histoplasma antibodies was positive in all but one case (Case III). During the five years of observation in this case there was no change in the cavitary lesion which might suggest activity of the lesion; there was, however, evidence of calcium deposition in the wall of the cavity com-

patible with healing. All the complement fixing antibody titers were only mildly or moderately elevated. Significance was attached to even the initial 1:2 serum dilution of histoplasma antibodies.

Follow-up. Since all these individuals, except one, were thought at first to have tuberculosis. they were treated for such in the sanatorium over varying periods of time. All gained weight and had reduction in the amount of sputum expectorated daily. All the patients, with the exception of four (Cases II, III, x and XI) have been productive of sputum from which H. capsulatum could be easily and regularly isolated throughout the course of their illness. Some of these patients have shown progression in their pulmonary lesions. Others have remained stationary or fluctuated between extension and regression of the lesion. As an exception, one patient (Case xi) has had complete healing of this cavitary lesion recently.

Two patients (Cases v and vII), died in December 1956, the former from arteriosclerotic heart disease and the latter probably from a cerebrovascular accident. One patient (Case IV) has shown marked progressive extension of his lesions associated with massive hemoptysis and profuse quantities of sputum expectorated daily. One patient (Case 1) died as a result of a gastric hemorrhage twenty days after lobectomy. Two patients (Cases II and VI) are clinically well at present, but the positive complement fixation titers indicate that the disease process in the lungs is still active. Four others (Cases VII, IX, xII and XIII) have apparently been cured by lobectomy, as indicated by absence of the lesion by roentgenographic examination, negative cultures, improved physical state and complement fixation titers falling toward the negative. Only one patient (Case XIII) was treated with amphotericin B before surgical resection, resulting in presurgical sterilization of his sputum. Another patient (Case x) has been asymptomatic and has had some clearing of his pulmonary lesion, and falling of the complement fixation titer without specific therapy. One patient (Case VIII) has a unilateral lesion which was thought to be suitable for resection, but he refuses to have anything done because of his

From the data in Table v, the complement fixation test is demonstrated to be an excellent procedure for the diagnosis and prognosis of chronic cavitary histoplasmosis. With the ex-

TABLE VI
AGE RANGE OF REPORTED AND AUTHORS' CASES OF
CAVITARY HISTOPLASMOSIS—EIGHTY-SIX CASES

Cases	Age (yr.)									
Cases	20-29	30-39	40-49	50-59	60-69	70-79				
Reported Authors'	3	14	18	20 6	16 2	2 2				
Total	3	14	21	26	18	4				

Table VIII

DURATION OF ILLNESS BEFORE DETECTION OF
CAVITARY HISTOPLASMOSIS (REPORTED CASES—60;*

AUTHORS' CASES—13†)

_		780	1110	100			211				
1	2	3	4	5	6	7	8	9	10	11	12
				Mo	nths						
8 2	6	6 2	1	1	6 2	0	0	0	1	1	
				Ye	ars						
7	6	5		2	3		2			1	1
	8 2 7	8 6 2	8 6 6 2 2	1 2 3 4 8 6 6 1 2 2	1 2 3 4 5 Mo	1 2 3 4 5 6	1 2 3 4 5 6 7	1 2 3 4 5 6 7 8	Months 8	Months 8 6 6 1 1 6 0 0 0 1	Months 8 6 6 1 1 6 0 0 0 1 1 1 2 2 1 Years

^{*} One twenty years, one twenty-four years, one thirty years.

ception of one patient (Case III) all had significant antibodies to the whole yeast histoplasma antigen. The most notable feature was the persisting, plateau-pattern of complement fixation antibody titers when chronic disease extended over a few months to as long as eight and a half years. The elevation of the titer was not generally significant. Surgical resection of the unilateral lesion in three cases (Cases VII, IX, and XII) produced a rather prompt drop in antibody titer. This is comparable to the course of acute histoplasmosis which heals spontaneously. Spontaneous healing of cavitary disease, as demonstrated by falling complement fixation titers in Cases X and XI, seems likely.

REVIEW OF THE LITERATURE

The thirteen cases of chronic cavitary histoplasmosis presented in this paper closely resemble the seventy-three cases which have been previously described in detail [26,28,39,55–85].

Table VII
SEX AND RACE OF REPORTED AND AUTHORS' CASES
OF CAVITARY HISTOPLASMOSIS—EIGHTY-SIX CASES

Cases	M	ale	Female			
Cases	White	Negro	White	Negro		
Reported	63 12	2 0	7	1 0		
Total	75	2	8	1		

The age ranges are shown in Table vi, emphasizing the fact that this is an adult form of histoplasmosis, limited to the older age group. Eighty per cent of the patients were over forty years of age. Table vII demonstrates the predominance of the disease in the white male population. The infection occurred approximately nine times more frequently in males than females. Only three patients, two males and one female, were Negroes. At least a fourth of the patients were farmers or worked with the soil. The great majority were residents of the endemic area for histoplasmosis. The remainder had served tours of duty in Panama or South America. The duration of illness before coming under observation, shown in Table viii, ranged from one month to thirty years.

As seen in Table 1x, seventy-three of eightytwo patients tested (90 per cent) gave a positive skin test with histoplasmin. The usefulness of the histoplasmin skin test as a clinical tool in the cavitary form of histoplasmosis is much more substantial than indicated by the 23 per cent non-reactors noted in a series of cases reported previously [37]. Only forty-two of seventy-nine tested (53 per cent) were tuberculin-positive. Of the total number of patients, thirty-eight (44 per cent) gave positive skin tests to both histoplasmin and tuberculin antigens. The organism, H. capsulatum, was isolated in all cases, either by direct culture of the sputum, biopsy, surgical or autopsy specimen, or was identified microscopically in tissue. Tubercle bacilli were cultured from eleven of the eightysix patients, thus indicating a dual infection in 8 per cent of the cases. The complement fixation test was positive for histoplasma antibodies in sixty-one of the seventy-five patients (81 per cent) in whom it was performed.

[†] One sixteen years.

276

Table ix

Skin tests, cultures and serology on reported and authors' cases of cavitary histoplasmosis combined—eighty-six cases

		Skin	Tests		Presence of	Complement	
	Н	Т	В	C	H. capsulatum	Tubercle Bacillus	Fixation for H. capsulatum
Positive	73	42	1	2	86*	11	61
Negative	9	37	11	19	0	75	14
Not done	4	7	74	65	0	0	11

^{*} Sputum cultures, 68; biopsy or surgical cultures, 15; autopsy cultures, 1; organism identified in tissue, 2.

TABLE X
LOCALIZATION OF LESIONS IN REPORTED AND
AUTHORS' CASES OF CAVITARY HISTOPLASMOSIS—
EIGHTY-SIX CASES

Cases	Right Upper Lobe	Left Upper Lobe	Bilateral	Other
Reported	23	19	29	2*
Authors'	5	5	3	0
Total	28	24	32	2

^{*} Right lower lobe.

The localization of the pulmonary lesions is shown in Table x. The preference for the upper lung fields and bilateral involvement in chronic histoplasmosis is remarkable. More than onethird of the patients had bilateral infiltration and cavitation. Thirty-four of these patients were subjected to a right or left upper lobectomy or segmental resection, as shown in Table xi. All but seven of the thirty-four were cured or improved. Of those showing no improvement, one had recurrence of a cavity and the other two had bilateral involvement with histoplasmosis or tuberculosis. The four deaths were due to postoperative complications, three of these deaths occurring in the fifty-five to sixty year old age group.

Complete histories concerning symptoms and findings were not adequately given, but weight loss, fatigue, dyspnea, weakness and productive cough were frequently mentioned. Blood examinations, although rarely recorded, were generally normal. Sedimentation rates were slightly to moderately elevated.

TABLE XI
RESULTS OF LOBECTOMY OR SEGMENTAL RESECTION
FOR CHRONIC CAVITARY HISTOPLASMOSIS IN
REPORTED AND AUTHORS' CASES—THIRTY-FOUR
CASES

Age (yr.)	Cured	Improved	Not Improved	Died *
20-24	1		* *	
25-29	2			
30-34	2			
35-39	6		1†	
40-44	2		2‡	
45-49	4	1		1
50-54	4	1		* *
55-60	4			3
Total	25	2	3	4

^{*} All postoperative deaths: hemorrhage, pulmonary embolism and gastrointestinal bleeding.

Only five of the total number of patients have had dissemination of the disease from the chronic cavitary lesions, resulting in death. Lack of proper follow-up makes it impossible to gauge accurately the regressive, static or progressive nature of the chronic lesion in each case. However, the disease is certainly not altogether a progressive one.

COMMENTS

The pathogenesis of active cavitary pulmonary histoplasmosis is not clear. The great majority of patients reported on in the literature, as well as those in this series, lived in the geographic area of high histoplasmin sensitivity.

[†] Recurrence of cavitation.

[‡]One had bilateral tuberculosis; one bilateral histoplasmosis.

Thus they most likely acquired their sensitivity or a primary infection at an early age. From the available evidence, non-fatal primary pulmonary infections heal completely, resulting in eradication of the organism from the lesions. Some authors have considered the cavitary cases described in this report to be reactivation histoplasmosis, such as is seen in tuberculosis. However, there is no evidence that pulmonary histoplasmosis, once healed by fibrosis and calcification, becomes reactivated. Reinfection is the more plausible explanation. All these persons have had an opportunity to become reinfected from an environmental source and most of them bear evidence of primary calcified lesions in the hilar area.

Many patients with cavitary histoplasmosis have also been shown to have active pulmonary tuberculosis, the histoplasma fungus being considered a secondary invader. Which infection occurred first cannot be determined in many cases. The tuberculosis sanatorium has been the usual destiny of patients with newly discovered cavitary histoplasmosis, misdiagnosed as tuberculosis, thus possibly inviting infection with the acid-fast bacillus. Secondary necrotizing exudative histoplasma lesions can explain the cavitation seen in most of these persons.

Treatment of pulmonary cavitary histoplasmosis with chemotherapeutic agents and antibiotics has been disappointing [86]. Further studies with a number of specific agents appear warranted. A favorable effect on the course of a few human infections and experimental infections in animals have been reported with sulfonamides, ethyl vanillate, beta-diethylaminoethyl fencholate, nystatin, disulfiram and a chemical bistertiary amine (amebacide) alone or in combination with other drugs.

The most promising therapeutic agent at present is amphotericin B. The use of amphotericin B combined with the surgical removal of the localized cavitary lesion provides the patient with the best therapy available. Surgical intervention alone offers promise of cure in carefully selected unilateral lesions.

SUMMARY

The clinical and laboratory characteristics of thirteen patients with chronic active pulmonary histoplasmosis are described. They were all initially considered to have tuberculosis; and indeed the roentgenographic findings and clinical manifestations are indistinguishable from tuberculosis.

Treatment in selected cases, as in tuberculosis, can be successfully carried out by surgical resection of the lesions. With the exception of amphotericin B, drug therapy has not been proved effective in patients with bilateral cavitation.

In areas of high endemicity, physicians and health workers should be alerted to the fact that many cases of histoplasmosis may be found in tuberculosis sanatoriums.

ADDENDUM

Since this paper was submitted for publication, several notable presentations of cases of chronic pulmonary histoplasmosis have appeared in print. Takaro et al. [87] reviewed five cases of cavitary disease, four of which were treated with surgical resection and the other with thoracoplasty. Only one of these patients died following resection. It was necessary to perform pneumonectomy on one patient for combined histoplasmosis and tuberculosis. The four patients surviving surgical therapy were considered cured.

Ninety patients with chronic pulmonary histoplasmosis, seventy-eight of whom revealed cavities by roentgenographic examination, were presented by Rubin et al. [88]. Many of these cases, which have previously been reported in detail, are included in our review. Surgery was performed upon a total of nineteen patients. The disease proved fatal to sixteen patients, four of whom died following surgery. Thirteen per cent of the patients were proved to have both tuberculous and histoplasma infections. The histoplasmin skin tests were negative in 20 per cent of the cases, and negative serological reactions persisted in 9 per cent of the cases.

Eight additional patients with chronic cavitary histoplasmosis resembling tuberculosis were reported by Conrad et al. [89]. All but one of the patients demonstrated positive serologic tests for histoplasmosis. Successful surgical resection was performed upon two patients. Another patient died, although a course of amphotericin B had been administered. Since a diagnosis of tuberculosis was originally made on the majority of these patients, antituberculous therapy had been given to six.

In our own studies, two of the patients (Cases rv and vi) with bilateral cavitary disease have maintained constant complement fixation titers

of 1:64 and 1:32, respectively, for an additional year. (Table v.) The remarkable regression and healing of the cavitary disease in Case XI has been further substantiated by the negative complement fixation test obtained since this paper was written.

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The Postpneumonectomy State*

Clinical and Physiologic Observations in Thirty-Six Cases

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the effects of extensive pulmonary resection on the anatomy and physiology of the remaining lung. Most of these studies have been concerned with the early postoperative period [1-3] or have stressed one particular aspect of the physiologic status [2,4]. In other instances, patients had been subjected to surgery during childhood [5-7], and there is reason to suspect that such cases are not comparable to pneumonectomy in the adult [8-11]. Only a few cases have been reported in which extensive studies were carried out many years after the performance of pneumonectomy in adult life.

The present review of clinical and physiologic findings in thirty-six postpneumonectomy patients was undertaken to define more clearly the abnormalities to be expected after extensive pulmonary resection and to determine those factors which lead to an occasional unsatisfactory physiologic result. It was hoped also that knowledge of the normal regulation of lung function might be furthered by observing the effects of removal of half the functioning lung.

MATERIALS AND METHODS

Case Material. Thirty-six postpneumonectomy patients seen in the Pulmonary Function Laboratory of the University of Chicago are included in the present report. Ten patients were studied during their first postoperative year. The remaining twenty-six were examined at least two years after surgery, and sixteen were examined five or more years after pneumonectomy. All patients had been subjected to pneumonectomy during adult life. Subjects studied are not necessarily a random sample of postpneumonectomy patients. The series is weighted toward subjects with restriction in exercise tolerance.

Pulmonary Function Tests. Routine spirographic determinations were obtained in all cases, including the vital capacity, first second vital capacity and maximal mid-expiratory flow [12]. The maximum breathing capacity was determined by the closed circuit method, utilizing a 13 L. Collins Respirometer. Normal values were determined on the basis of Baldwin's equations [13].

The residual volume was determined by a modification of the Darling open circuit technic [14], and normal values for the residual volume and total lung capacity were determined from the following ratios found applicable in our laboratory: for age groups fifteen to thirty-four, thirty-five to forty-nine, fifty to sixty-four, and over sixty-four, the predicted values of VC:TLC were taken as 0.8, 0.75, 0.65, and 0.6, respectively. A nitrogen washout curve was obtained using a nitrogen analyzer (Waters Corporation) and the uniformity of ventilation was assessed by determination of the pulmonary clearance delay, using a modification of the method of Fowler et al. [15]. In this modification, end tidal nitrogen values were used instead of integrated single breath curves.

Arterial oxygen saturation was determined with a continuously recording ear oximeter [16]. Routine determinations were made with the subject at rest breathing air and then breathing oxygen, and during exercise while breathing room air. Exercise consisted of stepping up and down a 9 inch step thirty times over a period one and a half to two minutes.

The pulmonary diffusing capacity was measured by the modification of the Krogh breath-holding technic described by Forster et al. [17], and reported values represent an average of two or three determinations for each subject. All determinations were made with the subject at rest; attempts to measure the pulmonary diffusing capacity during exercise were unsuccessful in these patients, utilizing the breath-holding method.

Cardiac Catheterization. Twenty-three patients were hospitalized for cardiac catheterization. Since cathe-

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TABLE I CLINICAL DATA

				CLINICAL	DAIA			
Case No.	Sex	Age at Surgery (yr.)	Side of Surgery	Operative Diagnosis	Associated Surgery	Age at Study (yr.)	Years Post- operative	Associated Disease*
				Group	A			
1	M	53	R	Abscess	None	53	3 mo.	None
	M	56	L	Carcinoma	None	56	2 mo.	ASHD
2 3	M	52	L	Carcinoma	None	52	13 days	None
4	M	56	R	Carcinoma	None	57	7 mo.	None
5	M	52	L	Carcinoma	None	53	1 yr.	Non-pulmonar metastases, ASHD
6	F	40	R	Metastatic carcinoma of breast	None	41	8 mo.	Non-pulmonar metastases
7	F	51	R	Carcinoma	Thoracoplasty	51	7 mo.	None
8	M	66	L	Carcinoma	Resection of chest wall	66	17 days	Non-pulmonar metastases
9	M	50	L	Carcinoma	None	50	11 days	None
10	M	53	R	Carcinoma	Pericardectomy	53	4 mo.	HCVD
Average		53				53	4 mo.	
				Group	В			
11	M	18	L	Cystic disease	None	25	5	None
12	M	61	R	Carcinoma	None	68	7	None
13	F	34	L	Tuberculosis	None	37	3	None
Average		38	* *			43	5	**********
		1		Group	C			
	1 1	1		Group	1 1			
14	F	40	R	Tuberculosis	Thoracoplasty	44	4	None
15	M	57	L	Carcinoma	None	69	12	None
16	M	36	R	Adenoma	Thoracoplasty	42	6	Rheumatic hea disease
17	M	56	L	Carcinoma	None	65	9	None
18	F	36	R	Adenoma	None	44	8	None
19	M	42	R	Carcinoma	None	49	7	None
20	F	30	R	Adenoma	None	39	9	None
21	M	39	R	Carcinoma	Thoracoplasty	45	6	None
22	M	59	R	Cystic disease	None	63	3.5	None
23	M	54	R	Abscess	None	57	3.5	None
24	M	55	R	Carcinoma	None	60	5	None
25	M	63	R	Carcinoma	None	65	2	Aortic stenosis
26	M	49	R	Carcinoma	None	52	3	None
27	M	50	L	Carcinoma	None}	57	7.5	None
Average		48				54	6	**********
				Group	D			
28	М	43	R	Carcinoma	Pericardectomy	48	5	Recurrent asthmatic bronchitis
29	M	59	L	Carcinoma	None	71	12	HCVD, ASHD
30	M	47	R	Carcinoma	Thoracoplasty	63	15.5	Silicosis
31	M	59	L	Carcinoma	None	62		Tuberculosis o remaining lung
32	M	60	R	Carcinoma	None	64	3.5	None
		54				62	8	

TABLE I (Continued)

				CLINICAL	DAIA			
Case No.	Sex Age at Surgery (yr.) Side of Surgery				Age at Study (yr.)	Years Post- operative	Associated Disease*	
				Group	E			
33	M	65	L	Carcinoma	Resection of chest wall	68	3	Pulmonary metastases
34	M	43	R	Carcinoma	None	60	17	Aortic stenosis
35	M	45	R	Carcinoma	None	56	11	None
36	M	67	L	Carcinoma	None	74	7.5	None
Average		55				65	10	
Average for all groups		50				55	5	

* ASHD = Arteriosclerotic heart disease.

HCVD = Hypertensive cardiovascular disease.

terization of the pulmonary artery was not technically feasible in all subjects, right heart systolic pressures are reported. Pressure measurements were made with a Statham strain gauge and Grass polygraph recorder. After obtaining the right heart systolic pressure with the patient in the supine position, the subject was asked to exercise by bicycling against a resistance for a three- to five-minute period. Unfortunately, the severity of exertion was not well controlled during the early part of the study. Cardiac output was determined simultaneously with the pressure measurements in twelve patients; arterial and venous blood gases were determined by the Van Slyke technique [18], and cardiac output was calculated by the direct Fick method.

Clinical and Pathologic Studies. A chest roentgenogram and electrocardiogram were obtained routinely. In ten cases repeat electrocardiograms were taken during exercise and while breathing oxygen. Exercise tolerance was determined on the basis of history and patients were arbitrarily divided into five groups. Group A consists of ten patients studied within their first postoperative year. The remaining twentysix patients were studied more than two years after surgery and have been divided into four groups on the basis of exercise tolerance: group B contains three patients who denied dyspnea even on moderate exertion. Group C consists of fourteen patients who complained of mild dyspnea on moderate exertion but who experienced no limitation of their normal activities. Group D contains five patients with moderate respiratory distress on exercise, and group E includes four patients with dyspnea at rest. Physical characteristics and operative diagnosis for all subjects are recorded in Table 1. Cases

are arranged alphabetically within the various groups.

Surgical specimens obtained at pneumonectomy were reviewed by one of us (E. M. H.) without prior knowledge of clinical results. Particular attention was directed to the state of those portions of lung not involved by the primary disease. In this way, some indication of an underlying chronic lung disease might be uncovered, especially in regard to emphysema and diffuse fibrosis.

OBSERVATIONS

Results of physiologic and clinical studies are summarized in Tables I, II and III. Review of surgical specimens obtained at pneumonectomy revealed the findings listed in Table IV. This list is incomplete since areas free of primary disease could not be found in some specimens, and pathologic material was not available for review in several instances.

Group A. These ten patients, studied during their first postoperative year, have not been tabulated in relation to exercise tolerance since dyspnea is difficult to evaluate during this early period. The average total lung capacity for these patients is 59 per cent of predicted, only slightly greater than that predicted for a single remaining lung. The residual volume is considerably elevated compared with the small vital capacity, and the RV:TLC ratio is, therefore, moderately increased. Expiratory slowing is absent or slight. The maximum breathing capacity is reduced considerably in all group A patients studied. No significant abnormality in

the distribution of inspired gas is noted in the nitrogen washout curves obtained, and arterial oxygen saturations at rest and on exertion are normal in the few patients studied. The pulmonary diffusing capacity is reduced to about 50 per cent of predicted values and in one case (Case 3) to approximately 50 per cent of the preoperative level. Cardiac catheterization was performed in only two patients in this group; both show a normal resting right heart systolic pressure and a moderate rise in pressure with exertion. Roentgenograms reveal slight to moderate overinflation of the remaining lung, except one patient (Case 5) in whom the overinflation is marked. Electrocardiograms reveal abnormal P waves in two patients, one with a normal right heart systolic pressure.

Groups B and C. The average age of these patients with normal or nearly normal exercise tolerance more than two years after pneumonectomy is somewhat lower than for the series as a whole, both at the time of surgery and at the time of study. Nine of these seventeen patients were operated upon for pulmonary carcinoma, the remainder for non-malignant disorders. Two patients show auscultatory evidence of valvular heart disease, but in neither instance is there cardiomegaly or symptomatology referable to the cardiac disease. The total lung capacity is definitely higher in this group than in group A due to an increased vital capacity. The residual volume is only slightly higher than in group A; thus, the RV:TLC ratio is lower, only slightly above the expected value for the age group studied. Expiratory slowing is either absent or slight except in two instances, and the maximum breathing capacity, although reduced, is slightly higher than in the early postoperative group. The delay in pulmonary clearance of nitrogen is within normal range in most patients studied. Considering the age of the patients, only two subjects (Cases 11 and 13) reveal an abnormal degree of non-uniform ventilation. These two patients show the greatest overinflation of their remaining lung, and both reveal herniation of lung across the mediastinum. It seems possible that mechanical factors within the thorax prevent normal intrapulmonary gas distribution. Over-all emptying of the lung is not impaired as manifested by an RV:TLC ratio of only 24 per cent in Case 11.

Arterial oxygen saturation at rest is normal in the nine patients studied and reveals no significant fall on exercise in seven (a fall of less than

2 per cent is within normal limits in this laboratory). The borderline decrease in arterial oxygen saturation on exertion in two patients (Cases 14 and 23) is difficult to interpret, although in one patient (Case 23), there is a particularly low pulmonary diffusing capacity. The pulmonary diffusing capacity is close to predicted in only one of nine patients studied; this was the youngest subject in the entire series. Two other subjects show pulmonary diffusing capacities near the lower limit of normal; the remaining six patients reveal definitely reduced pulmonary diffusing capacities, averaging about half the predicted value. The resting right heart systolic pressure was determined in fourteen instances. It is above 25 mm. Hg in ten, but above 35 in only two. In each subject there is a definite rise in pressure on exertion, with recorded values as high as 86 mm. Hg.

The electrocardiogram is normal in nine of sixteen patients. Non-specific T wave abnormalities are noted in two. Two other patients reveal a pattern consistent with left ventricular hypertrophy. A right bundle branch block is noted once in association with a prolonged P-R interval in a patient with physical findings of aortic stenosis. Abnormal P waves are noted in three subjects and this abnormality is not correlated with the right heart systolic pressure.

Lung size as judged radiographically correlated only crudely with total lung capacity determinations. Herniation of the lung across the mediastinum was noted in three instances, two of which are shown in Figure 1. These subjects, with massive overinflation of their remaining lung, were among the best in terms of exercise tolerance.

The three patients in group C who had a thoracoplasty reveal an average total lung capacity of 69 per cent and a residual volume of 88 per cent of predicted, values almost identical with the average of group C as a whole.

In only seven instances was adequate pathologic material available to assess the status of the lung not involved by the primary disease. Three revealed a normal lung in areas remote from the primary disease. Two subjects showed slight fibrotic changes with anthracotic deposits reminiscent of anthracosilicosis (called "pneumoconiotic fibrosis" in Table IV). These two revealed borderline emphysematous changes. Another subject showed borderline changes of "hypertrophic" emphysema without significant fibrosis, and the seventh patient revealed

TABLE II
PULMONARY FUNCTION TESTS

	Total Lung	Vital	Residual	Residual Volume/ Total	% Vital	Maximal Mid-	Maximum Breathing	% Pul- monary		erial O2 uration	
Case No.	Capacity (% pred.)	Capacity (% pred.)	Volume (% pred.)	Lung Capacity (×100)	Capacity (in 1 sec.)	Expiratory Flow (L./sec.)	Capacity (% pred.)	Clearance Delay	At Rest	Fall on Exercise	DL/M ²
				(Group A						
1		52			67	1.0					
2 3	65	46 48	95	51	80 93	1.5		30	97	1.0	7.7
4	55	46	67	43	89	1.5	52	75	96	1.0	6.7
5	65	47	92	49	70	0.9	37	37	95	0	5.7
6	57	42	90	41	98	2.0	53	40			
7 8		52 64	* * * *		80 59	0.6	47 59				
9	55	45	72	46	81	1.8	49				
10		35			64	0.8	42				
Average	59	48	83	46	78	1.3	48	46	97	0.7	6.7
	1			G	Group B						
11	96	91	114	24	70	2.4	82	88	97	0	15
12	58	48	63	44	77	1.7	48	21			
13	97	68	150	39	74	1.9	59	72	98	0	9.8
Average	83	69	109	36	74	2.0	63	60	98	0	12.4
				G	roup C						
14	68	54	82	37	62	0.6	33	51	98	2.5	8.5
15	68	59	62	41	69	1.2	40	41			****
16 17	66	56 72	93	36	81 76	1.7	45 72	44			* * * *
18	90	67	156	44	70	1.6		36	97	0	6.7
19	67	59	83	32	89	2.4	61	78			
20	71	54	116	42	73	0.9	34	59			
21	72	64	89	32	77	1.6	49	46			
22 23	81	62	99 70	45	80 98	1.7	84 56	73	96	2.0	11.5
24	56 70	45 62	86	43	69	1.0	54	48	98	0	4.4 7.7
25	59	57	62	41	88	3.0	46	73	99	0	6.1
26	66	64	68	34	70	1.7	52	89			
27	72	57	100	49	78	1.5	63	48	97	1.5	10.4
Average	70	59	90	40	77	1.6	53	55	98	0.9	7.9
				Gı	roup D						
28	76	42	162	54	63	0.6	31	71	95	1.0	8.8
29	72	63	85	48	54	0.6	30	120	95	3.0	6.4
30	50	34	80	57	71	0.5	34	47	94	0	4.9
31	88	55	134	57	56	0.8	33	184	98 97	1.5	9.0
32	71	45	119	59	78	1.2	39	107			4.2
Average	71	48	116	55	64	0.7	33	106	96	1.5	6.7
			-	Gr	oup E	1	1			-	
33	67	31	105	63	74	0.6	22	134	93	7.0	
34		35			66	0.4	32				
35	55	24	104	66	50	0.5	17	128	95	1.5	
36	103	75	147	54	46	0.6	43	150	96	8.0	4.0
Average	75	41	119	61	59	0.5	29	137	95	5.5	4.0
Average for all groups	70	53	98	45	73	1.3	47	72	97	1.6	7.6

^{*}DL/M² = Pulmonary diffusing capacity for carbon monoxide in cc./min./mm. Hg per square meter of body surface area (normal range in this laboratory 10 to 18).

FEBRUARY, 1960

TABLE III
RESULTS OF ELECTROCARDIOGRAMS, CHEST ROENTGENOGRAMS AND CARDIAC CATHETERIZATIONS

1 Abnormal 2 Abnormal 3 Abnormal 5 Healing my infarct 6 Normal 8 Abnormal 10 LVH Average 11 Normal 12 Abnormal 13 Normal 14 Abnormal 15 Infarct 16 Abnormal 17 Abnormal 18 Normal 19 Normal 10 Normal 10 RbBB, 1 deg	P T	Over- Inflation	Hernia of Lung	Lesions Remaining Lung				Cardiac Index (L./M²)	
2 Abnormal 3 4 Abnormal 4 Abnormal 5 Healing my infarct 6 Normal 8	T			23000	Rest	Exercise	Rest	Exercis	
2 Abnormal 3	T		Group A						
2 Abnormal 3 4 Abnormal 5 Healing my infarct 6 Normal 10 LVH Average 11 Normal 12 Abnormal 13 Normal 14 Abnormal 15 16 Abnormal 16 PVC 17 LVH, PVC 17 LVH, PVC 18 Normal 19 Normal 19 Normal 19 Normal 20 Normal 21 Normal 22 Normal 23 Abnormal F	T	++	0	None					
3 4 Abnormal Healing my infarct Normal Normal LVH Average Normal Abnormal LVH Average Abnormal Normal	1	+	0	None					
4 Abnormal 5 Healing my infarct 6		+	0	None					
5 Healing my infarct 6			1		20	21	* * *	4.1	
Infarct		++	0	None	28	31	2.0	1	
10	yocardial	+++	0	None	25	39	3.8	4.2	
7 8 9 10 10 10 10 10 10 10 10 10 10 10 10 10		++	0	None	* *	* *			
10		++	0	None					
9				1		4. 4.		***	
10 LVH Average		+	0	None	6.8			43.8	
11	Г	++	0	None					
11 Normal 12 Abnormal 13 Normal Average 14 Abnormal I 15 16 Abnormal I PVC 17 LVH, PVC 18 Normal 19 Normal 19 Normal 20 Normal 21 Normal 22 Normal 23 Abnormal I Normal 24 Normal		+	0	None					
12 Abnormal 1 Normal Average 14 Abnormal I 15 16 Abnormal I PVC 17 LVH, PVC 18 Normal 19 Normal 19 Normal 20 Normal 21 Normal 22 Normal 23 Abnormal I Normal 24 Normal					27	35	3.8	4.2	
12 Abnormal 1 13 Abnormal 2 14 Abnormal 1 15			Group B						
12 Abnormal 1 13 Abnormal 2 14 Abnormal 1 15		+++	+	None					
13 Normal Average 14 Abnormal I 15	T	TTT	0	None	* *	* *			
14 Abnormal I 15	1	+++	+	Small calcific	25	41	3.1	5.3	
15 16 Abnormal I PVC 17 LVH, PVC 18 Normal 19 Normal 20 Normal 21 Normal 22 Normal 23 Abnormal F Normal		*****			25	41	3.1	5.3	
15 16 Abnormal I PVC 17 LVH, PVC 18 Normal 19 Normal 20 Normal 21 Normal 22 Normal 23 Abnormal F Normal			Group C	1					
16 Abnormal I PVC 17 LVH, PVC 18 Normal 19 Normal 20 Normal 21 Normal 22 Normal 23 Abnormal F	P	++	0	Small fibrotic	22	39	3.6	4.8	
16 Abnormal I PVC 17 LVH, PVC 18 Normal 19 Normal 20 Normal 21 Normal 22 Normal 23 Abnormal F				lesion		10			
PVC 17 18 Normal 19 Normal 20 Normal 21 Normal 22 Normal 23 Abnormal F 24 Normal		++	0	None	33	48			
17 18 Normal 19 Normal 20 Normal 21 Normal 22 Normal 23 Abnormal F Normal	P, LVH,	+	0	None	35	70	* * *		
18 Normal 19 Normal 20 Normal 21 Normal 22 Normal 23 Abnormal 24 Normal		++	0	None	34	66			
19 Normal 20 Normal 21 Normal 22 Normal 23 Abnormal F 24 Normal	-	+++	+	None	34	43	3.2	3.5	
20 Normal 21 Normal 22 Normal 23 Abnormal F 24 Normal									
21 Normal 22 Normal 23 Abnormal F 24 Normal		++	0	None	30	40			
22 Normal 23 Abnormal F 24 Normal						**		* * *	
22 Normal 23 Abnormal F 24 Normal		0	0	None	21	43		* * *	
23 Abnormal F 24 Normal		+	0	None	22	34	2.6	4.8	
24 Normal	>	++	0	None	33	42			
		+	0	None	39	86			
block, wa	indering	+	0	None	33				
pacemaker			0	None	35	55			
26 Normal 27 Abnormal T		++	0	None ? Fine fibrosis	35 41	55 75	2.6	5.7	
Average				2220 2275 0020	32	53	3.0	4.7	

Table III (Continued)
RESULTS OF ELECTROCARDIOGRAMS, CHEST ROENTGENOGRAMS AND CARDIAC CATHETERIZATIONS

Case No.	Findings on Electrocardiogram*	C	Chest Roentgenogram				Cardiac Index (L./M²)	
	Electrocardiogram	Over- Inflation	Hernia of Lung	Lesions Remaining Lung	Rest	Exercise	Rest	Exercise
			Group I)				
28	Normal	++	0	None	19	34	2.4	5.5
29	LVH, PVC	+	0	None				
30	Abnormal P, wan- dering pacemaker	0	0	Nodular fibrosis	38	56	1.8	3.6
31	Abnormal P, ? RVH	+++	0	Cavitary infiltrate	46	64	2.5	3.8
32	Abnormal P	++	0	None	48	65	2.2	3.0
Average					38	55	2.1	4.0
			Group E			1		
33	Abnormal P, abnormal QRS	++	0	Pleural effusion	34	56	2.1	1.8
34	Abnormal P	+	0	None				
35	Abnormal P	++	0	None	56	85		
36	Abnormal P	+++	0	None	75	112		
Average					53	84	2.1	1.8
Average for all groups					35	56	2.7	4.2

^{*} LVH = Left ventricular hypertrophy pattern; PVC = Premature ventricular contractions; RBBB = Right bundle branch block; RVH = Right ventricular hypertrophy pattern.

moderate "pneumoconiotic fibrosis" with moderate emphysematous changes. Clinical and physiologic studies do not reveal any distinctive abnormalities in this latter patient (Case 24).

Groups D and E. The age at time of surgery is higher on an average for these functionally restricted patients than for groups B and C; all patients in groups D and E were operated upon after the age of forty. A similar correlation exists between functional group and age at the time of study. Although the average time elapsed between surgery and study is longer in groups D and E than in the better functional groups, the spread of values is too great to be of real significance. These relationships are depicted in Figure 2.

No significant correlation can be found between functional result and sex of the subject, side of pneumonectomy, or operative diagnosis. Any seeming correlations are explained by age differences of the various groups.

As a whole, groups D and E reveal almost the same total lung capacities as group C, but have a higher residual volume, lower vital capacity, and much higher RV:TLC ratio. Both the satisfactory and unsatisfactory functional groups reveal greater overinflation of the remaining lung than in the early postoperative period; this overinflation is due to an increase in vital capacity in the better functional groups B and C and to an increase in residual volume in groups D and E. These effects are depicted in Figure 3. Serial roentgenograms confirm this gradual increase in lung volume after surgery, the remaining lung increasing in size concomitant with contraction of the operated hemithorax and shift of the mediastinum toward the operated side. (Fig. 4.) There is a high incidence of

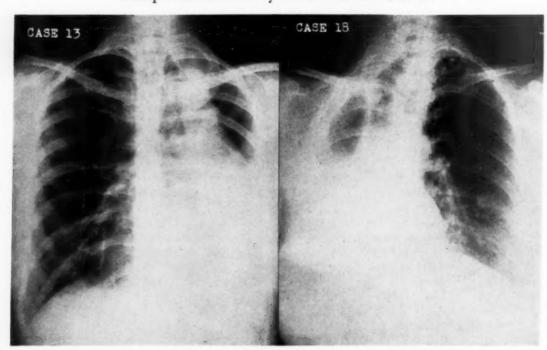


Fig. 1. Chest roentgenograms (Cases 13 and 18) revealing herniation of the remaining lung across the mediastinum.

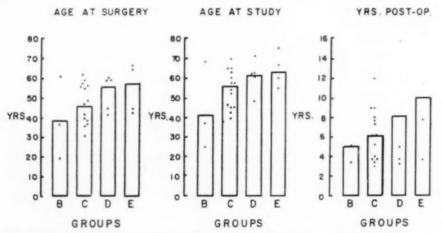


Fig. 2. Age at time of pneumonectomy, age at time of study, and years elapsed between pneumonectomy and study for patients in groups B through E. Vertical bars represent average values for each group.

associated disease in groups D and E. The poor exercise tolerance of four patients (Cases 28, 30, 33 and 34) may be explained by their complicating cardiopulmonary disorder.

Case 28. This patient with recurrent asthmatic bronchitis who has little or no dyspnea between attacks is included in group D because studies were performed during one of his episodes. His residual volume is markedly elevated as is his RV:TLC ratio, and there is moderately severe expiratory slowing. These marked abnormalities have been found to disappear after amelioration of his bronchitis. Even during the episode of dyspnea, there is no significant abnormality in the distribution of inspired gas, no

arterial oxygen unsaturation, and no resting pulmonary hypertension. His electrocardiogram is normal, and his pulmonary diffusing capacity is about the same as subjects in group C. This patient would seem to fit better in group C except for his episodic bronchitis with bronchospasm.

Case 30. This patient has a long history of exposure to silica dust and had x-ray evidence of diffuse silicosis prior to surgery. He shows the smallest total lung capacity of the entire series and his high RV:TLC ratio is a function of the markedly reduced vital capacity. There is some expiratory slowing but no significant non-uniformity of ventilation. The arterial oxygen saturation is borderline at

TABLE IV
REVIEW OF SURGICAL SPECIMENS

	REVIEW OF SURGICAL SPECIMENS
Case No.	Surgical Specimens Obtained at Pneumonectomy: State of Lung Remote from the Primary Disease
	Group C
18	Normal
19	Slight pneumoconiotic fibrosis; slight emphysema
20	Normal
22	Normal
24	Very slight pneumoconiotic fibrosis; ? early emphysema
26	Moderate pneumoconiotic fibrosis; moderate emphysema
27	Questionable early obstructive emphysema
	Group D
28	Moderate pneumoconiotic fibrosis; moderate emphysema
29	Frank obstructive emphysema
30	Frank silicosis
31	Moderate pneumoconiotic fibrosis; moderate emphysema
32	Frank obstructive emphysema
	Group E
33	Frank obstructive emphysema
35	Very slight pneumoconiotic fibrosis; no emphy- sema
36	Frank obstructive emphysema

rest and shows no fall on exertion. The pulmonary diffusing capacity is markedly reduced, and there is slight right heart hypertension at rest with a moderate increase in pressure on exertion. The electrocardiogram shows P wave abnormalities. The entire picture seems consistent with silicosis of a single remaining lung. This patient had a postoperative empyema necessitating thoracoplasty; his relatively small remaining lung may be partly related to these events. At any rate, there is evidence of restriction of the remaining pulmonary vascular bed and marked impairment of pulmonary diffusion, both of which may be due to the pneumoconiosis.

CASE 33. This patient displayed a pleural effusion at the time of study; his subsequent downhill course and postmortem findings confirm the presence of pulmonary metastases at that time. There was clinical evidence of a cor pulmonale. Pulmonary function tests revealed a markedly elevated residual volume and RV:TLC ratio, abnormal intrapulmonary mixing, marked expiratory slowing, and arterial oxygen

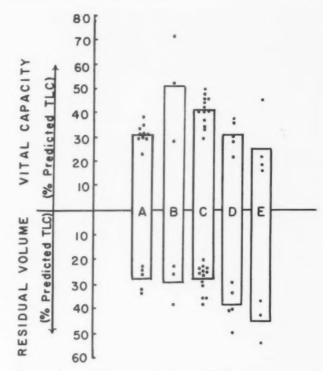


Fig. 3. The vital capacity is expressed as per cent of predicted total lung capacity and plotted above the horizontal line. The residual volume, also expressed as per cent predicted total lung capacity, is plotted below the horizontal line. The vertical bars represent average values for each group, and their total height indicates the total lung capacity expressed as per cent predicted for a normal subject.

desaturation on exertion. The findings are compatible with an obstructive emphysema in addition to the effects of the metastatic disease. The lung removed three years previously revealed evidence of obstructive emphysema in areas distant from the carcinoma; it must be assumed that this process was a contributory factor in his cardiorespiratory insufficiency, although, from the extensive metastases noted at autopsy, the tumor must be considered the major cause of death. Cardiac output studies revealed a slight fall in cardiac index on exertion, compatible with the clinical diagnosis of cardiac decompensation.

CASE 34. This patient is of particular interest. His postoperative course was uneventful for over twelve years, when he noted the first of a series of respiratory infections. During the next several years, congestive heart failure developed, leading to his death more than seventeen years after pneumonectomy. It had been assumed during life that the cardiac disease was on the basis of cor pulmonale. However, autopsy revealed an aortic stenosis with predominant left ventricular enlargement which was considered the primary cause of death. Some right ventricular enlargement was also noted but was of only moderate degree. It would seem that the cardiorespiratory

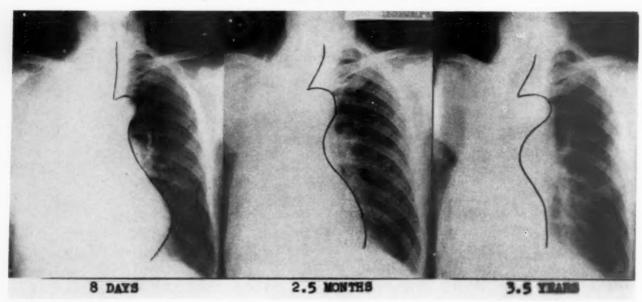


Fig. 4. Chest roentgenograms (Case 32) revealing enlargement of the remaining lung and contraction of the operated hemithorax following pneumonectomy. The left cardiac border is delineated by the superimposed dark line and time after surgery is indicated at the bottom of the films.

failure in this case cannot be traced directly to the effects of pneumonectomy.

Thus, associated disorders account for the decreased cardiopulmonary reserve in four of the nine patients in groups D and E. Of the five remaining, there is a complicating disorder in two (Cases 29 and 31) but in neither instance is this considered of major importance in producing the pulmonary insufficiency state. In Case 29 there was some cardiomegaly, mild hypertension, and runs of premature ventricular systoles. However, clear evidence of congestive heart failure could not be uncovered and the cardiac disease does not seem to explain the patient's chronically decreased exercise tolerance. In Case 30 there was a small cavitary infiltration which proved to be due to tuberculosis. This lesion appeared after the onset of dyspnea and is too small in extent to explain the patient's chronic exertional dyspnea. These two patients and three others (Cases 32, 35 and 36) reveal certain similarities in their clinical and physiologic findings. In all, the residual volume is elevated out of proportion to the total lung capacity, producing a high RV:TLC ratio. There is a definite abnormality in the distribution of inspired gas in all five patients and marked expiratory slowing in four of the five. A frank fall in arterial oxygen saturation on exercise is noted in two of the subjects with a borderline fall in a third. The pulmonary diffusing capacities are among the lowest

recorded in this series. Resting right heart hypertension is noted in the four patients studied and exercise systolic pressures are markedly elevated. Four of these five patients reveal P wave abnormalities on the electrocardiogram. All the findings are compatible with obstructive emphysema. In Case 36, there is clinical evidence of cor pulmonale and congestive heart failure. Three of these five subjects with postoperative findings suggesting emphysema revealed frank evidence of chronic obstructive emphysema in their original surgical specimens in areas remote from their pulmonary malignancy. An additional patient revealed moderate "pneumoconiotic fibrosis" with moderate emphysematous changes. In the fifth patient (Case 35), lung not involved by tumor was essentially normal. It would appear that the emphysema in four of these subjects antedated their pulmonary resection.

COMMENTS

The majority of patients studied revealed only mild dyspnea and were not handicapped as a result of their previous pulmonary resection. There was a moderate overinflation of the remaining lung which increased gradually during the first one or two postoperative years. This increase in lung volume was not appreciably affected by thoracoplasty or by immobility of the mediastinum as judged radiographically.

As a group, the relatively asymptomatic

patients revealed no evidence of airway obstruction, showed normal intrapulmonary mixing, and normal arterial oxygen saturation. Their physiologic abnormalities were only uncovered in studies of the pulmonary vasculature and pulmonary diffusing function. These results are in accord with previous reports of postpneumo-

nectomy lung function [1,2,3,19,20].

In only nine of the twenty-six patients studied more than two years after surgery was there an appreciable decrease in exercise tolerance and, in four of these, the disability may be explained on the basis of a complicating disorder (aortic stenosis, metastatic carcinoma, silicosis, and recurrent asthmatic bronchitis). In the five remaining patients, there was no obvious clinical explanation for the pulmonary disability, but physiologic studies indicate a process resembling idiopathic chronic obstructive emphysema.

Emphysema and the Postpneumonectomy State. There has been considerable speculation over the years concerning the development of true emphysematous changes in the remaining lung after extensive pulmonary resection. A number of investigators have concluded that destructive changes in the alveolar walls do occur as a result of chronic overdistention of remaining lung tissue, and these changes have been called "emphysema" despite lack of airway obstruction. Longacre and associates [9-11] on the basis of anatomic and physiologic studies in dogs, noted emphysema after pneumonectomy performed on adult animals. Phillips et al. [21] also described destructive changes in the alveolar walls following extensive pulmonary resection in adult dogs, although they termed the process "compensatory emphysema." Others have concluded from postoperative studies in man that deleterious changes of an emphysematous type may occur in the postpneumonectomy state and have speculated on the role of overdistention in producing such changes [1,3]. For a period, there was discussion of the value of thoracoplasty in preventing this supposed undesirable aftermath of chronic overdistention [7].

On the other hand, there is considerable evidence that the usual effect of pneumonectomy in adults is to produce only a simple overdistention of the remaining lung. Bremer [8] reported such findings after pneumonectomy in the adult cat. Rasmussen et al. [22] demonstrated only overdistention of the alveoli after moderate pulmonary resections in adult dogs, and other

investigators have interpreted their post pneumonectomy studies in man as failing to demonstrate destructive changes in the remaining lung after pneumonectomy [19,23]. Attempts to improve postresection lung function in the dog by space reducing procedures have not been successful [22,24].

The majority of the patients in the present report fail to demonstrate physiologic evidence of degenerative changes in their remaining lung and show responses about as predicted for an overinflated, but otherwise normal, single lung. We are led to conclude that emphysematous changes, if present, must be of minor degree in most patients who have sustained an extensive pulmonary resection, an opinion similar to that of Birath et al. [19]. It is apparent that massive overinflation of the remaining lung may occur without impairment of physiologic function, and that there is no relationship between total lung capacity and exercise tolerance. All patients revealed a moderate to marked increase in the residual volume but, in most, there was only a moderate increase in the residual volume: total lung capacity ratio. As has been pointed out by others, the presence of an elevated RV:TLC ratio does not necessarily indicate true emphysema; it may be due to a simple inability to collapse the thorax [19].

Patients with decreased exercise tolerance unexplained by associated disease revealed a much more marked elevation of residual volume and RV:TLC ratio than the rest of the group. Such subjects showed other evidence of chronic obstructive emphysema in addition to their lung volume changes, e.g., evidence of increased airway resistance, abnormal intrapulmonary mixing, arterial oxygen desaturation on moderate exertion, and markedly restricted pulmonary diffusing capacity. Since there is no significant difference in the over-all overinflation of the lungs (as reflected by the total lung capacities) between patients with a satisfactory and unsatisfactory functional result, it is difficult to believe that overdistention per se was directly responsible for the development of obstructive emphysema in the more disabled subjects. In addition, "obstructive" emphysema has never been noted following extensive lung resection in the experimental animal. Our findings in the more restricted patients cannot be explained by any known effect of simple pulmonary overdistention or "compensatory emphysema." Even more important, in four of the five patients

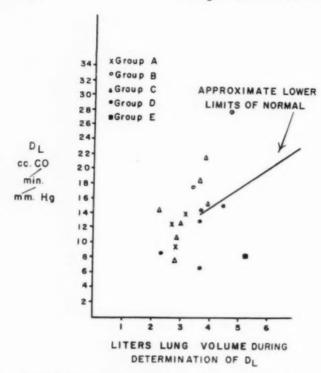


Fig. 5. Pulmonary diffusing capacity is plotted against the lung volume STPD (standard temperature and pressure, dry) at which the test was performed (approximately the total lung capacity in each case). The upper limit of normal range in this laboratory is approximately twice the lower limit indicated.

manifesting postoperative obstructive emphysema there were significant emphysematous changes in the resected lung, indicating that emphysema, although possibly aggravated by surgery, had developed prior to resection. For these reasons, we believe that an unsatisfactory cardiopulmonary status following pneumonectomy is a result of either a complicating disease or a pre-existing abnormality of the remaining lung. Since such abnormalities or complications are more frequent in older patients, a higher incidence of postpneumonectomy pulmonary insufficiency is to be expected with advancing age. The underlying pulmonary disorder may be aggravated by the effects of pneumonectomy, or its manifestations may be accelerated.

Pulmonary Diffusion and Perfusion at Rest Following Pneumonectomy. The right heart systolic pressure at rest was close to normal limits in most patients studied, and marked elevations were limited to those patients with an abnormal remaining lung. It is well recognized that pulmonary blood flow may be increased more than twofold during exercise before a rise in pulmonary artery pressure occurs in normal sub-

jects [25,26]. One may consider that blood flow through the remaining lung in a patient after pneumonectomy is approximately twice its normal value for the resting state since the entire cardiac output now flows through this single lung. Therefore, the essentially normal resting right heart pressure in the absence of abnormalities of the remaining lung is not surprising and has been previously noted in man as well as in the late postoperative experimental animal [4,20,27,28].

There is evidence that the effects of exercise and of occlusion or removal of pulmonary vessels may not be entirely comparable. Brofman et al. [29] have demonstrated a moderate rise in pulmonary artery pressure on occlusion of one main pulmonary artery in man. The magnitude of this rise was such that postocclusion values might have been considered within normal limits had no preocclusion pressures been available for comparison. Our values for the postpneumonectomy state may also represent a moderate increase in pressure at rest, too small to recognize without adequate controls. Lategola [30] has shown a rise in pulmonary artery pressure during partial occlusion of the pulmonary vascular bed in the experimental animal. An immediate postpneumonectomy rise in resting pulmonary vascular pressure in dogs has been noted by other observers [27]. These results indicate that the twofold increase in blood flow through the remaining vascular bed after occlusion or removal of half the functioning lung is accompanied by some elevation of pulmonary arterial pressure while a comparable increase in blood flow per unit of lung in normal subjects during exercise produces no such elevation.

An additional difference between the response of the pulmonary vascular bed during exercise and after resection of lung is noted in the pulmonary diffusing capacity (D_L). Our data and those of McIlroy and Bates [3] have indicated a fall in pulmonary diffusing capacity for carbon monoxide approximately proportional to the fall in lung volume for most postpneumonectomy subjects, and a more marked fall when there is an abnormality of the remaining lung. (Fig. 5.) We have observed a decrease in diffusing capacity to approximately half its preoperative value as an acute response to pneumonectomy. Cournand et al. have found normal pulmonary diffusing capacities in three of five postpneumonectomy patients studied by the oxygen method [20]. However, the three subjects with normal oxygen

diffusing capacities had been operated upon before the age of twenty-two, while the two abnormal patients were in an older age group at the time of surgery, more comparable to the patients presently reported. The present results, those of McIlroy and Bates, and those of Cournand in his two older subjects, are in sharp contrast to the reported results during exertion. Exercise is known to produce a marked increase in pulmonary diffusing capacity [31-33], an increase roughly correlated with the increase in pulmonary blood flow [34]. Doubling the pulmonary blood flow through one lung by removal of the contralateral lung fails to produce a significant increase in the diffusing capacity of the remaining pulmonary tissue; a comparable increase in blood flow during exertion in a normal person will increase D_L considerably.

It was the contention of Brofman et al. [29] that results with unilateral pulmonary artery occlusion supported the "critical closing pressure" concept of Burton [35,36] in regulating capillary circulation in the lung. This theory states in essence, that the total closing (or opening) of a capillary is solely dependent upon a sufficient transmural pressure, that "critical pressure" having a distinct value for each capillary at any level of vasomotor tone. Lategola [30] believed that the difference in pressureflow curves during partial vascular occlusion and during exercise was indicative of an active vasomotor effect during exertion, allowing sufficient decrease in pulmonary vascular resistance to prevent a rise in pulmonary artery pressure with increases in flow up to three times the resting value. Such vasomotor effects presumably were not operative during partial vascular occlusion. Our data in the postpneumonectomy patient also suggest that some active vasomotor component is operative during exertion in a non-pneumonectomized subject to allow an increase in pulmonary diffusing capacity, an increase presumably related to an enlargement of the active pulmonary capillary bed.

It is possible to explain the findings after occlusion or resection of part of the pulmonary arterial system on the basis of a passive reaction of the remaining vasculature. A slight rise in pulmonary artery pressure occurs, resulting in passive dilatation of the remaining lung vessels and some decrease in pulmonary vascular resistance. Due to the slight increase in pressure, some new capillaries are opened as a passive reaction according to Burton's theory, but this increase in

active capillary bed may be too small to be recognized in measurements of the pulmonary diffusing capacity. In this case, there must be an additional vasomotor reaction during exertion to explain the more profound fall in pulmonary vascular resistance and the more marked increase in pulmonary capillary bed. This response would apparently be more or less specific for the stimulus of exertion and not solely dependent on the increased pulmonary blood flow. Of course, the available data are explained equally well by a continuing vasomotor component which fluctuates in response to various stimuli.

It seems unlikely that the reduced pulmonary diffusing capacity after pneumonectomy is a result of anatomic changes in pulmonary vasculature. The acute fall in diffusing capacity with resection cannot be explained in this manner. In addition, such vascular changes would be expected to produce a distinct pulmonary hypertension at rest with a single remaining lung; six patients in the present series with pulmonary diffusing capacities averaging only 60 per cent of predicted, show right heart systolic pressures ranging from 19 to 28 mm. Hg.

Right Heart Systolic Pressure on Exertion Following Pneumonectomy. A rise in right heart systolic pressure is noted regularly on exertion in the postpneumonectomy state. In this regard, our results are in accord with previous reports in man and in experimental animal [4,20,27,28]. This rise in pressure on exercise is predictable on the basis of pressure-flow curves for human and animal lungs [20,29,30]. Despite the maintenance of a normal or nearly normal pulmonary artery pressure with increase in blood flow to almost threefold resting level, further increase in flow produces a marked increase in right heart pressure. In the case of a single remaining lung, in which resting flow is double its normal resting level, even a moderate increase in cardiac output will produce a sufficient flow rate to produce pulmonary hypertension. In such a range, the pulmonary artery or right heart systolic pressure will be directly related to cardiac output and the normality of a particular right heart pressure would be doubtful without simultaneous cardiac output determinations.

In Figure 6 the right heart systolic pressure is plotted against cardiac index for the eleven patients for whom sufficient data is available. A "normal curve for one lung" has been drawn in a manner previously employed by Cournand

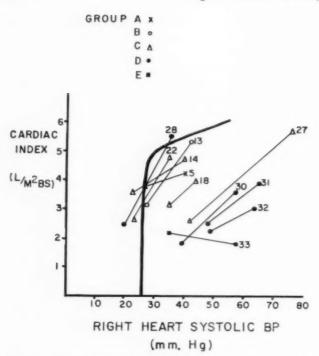


Fig. 6. The solid heavy line indicates a "normal curve" for one lung after Cournand et al. [46]. The two points for each subject represent rest and exercise values and case numbers are designated. See text for further explanation.

et al. [20]. It is apparent that most subjects in the better functional groups B and C fall close to "normal." The most glaring exception is Case 27; it is interesting that this patient showed the highest RV:TLC ratio in group C. It seems possible that early emphysematous changes and an abnormal remaining pulmonary vascular bed are developing. Values in other patients in groups B and C are even closer to those reported by Brofman et al. during occlusion of one main pulmonary artery in normal subjects [29]. Patients in groups D and E fall distinctly in an abnormal range of right heart pressure, with one exception (Case 28). This patient is classified as a poor functional result solely on the basis of recurrent episodes of asthmatic bronchitis. It is not surprising that he has a reasonably normal remaining pulmonary vascular bed. The pulmonary hypertension in the remaining subjects in groups D and E is evidence of a restricted pulmonary vascular bed. In two cases (Cases 31 and 32), this is the result of obstructive emphysema and in another (Case 30), the result of silicosis. In one patient (Case 33), the cardiac output and pulmonary artery pressures are compatible with his clinical diagnosis of cardiac decompensation.

Pneumonectomy has obviously produced a marked tendency to pulmonary hypertension. The flow through each lung would be reduced to half if both lungs remained in these subjects. From Figure 6 it is apparent that this should result in normal right heart pressures for most patients even on exertion, and much less elevated pressures in those patients with abnormal lungs (groups D and E). The perfusion function of the lung is particularly susceptible to the effects of resection, and it is not surprising that cor pulmonale has been noted as a major postoperative problem [37–40]. What is more remarkable is the ability of some patients to maintain significant elevations of right heart pressure for years without demonstrable evidence of right heart decompensation. Exertional pulmonary hypertension with normal or nearly normal pressures at rest is apparently unattended by clinical findings. These observations demonstrate, once again, the need for cardiac catheterization in the early detection of pulmonary hypertension and also point out that mild pulmonary hypertension, especially occurring only on exertion, is not necessarily a grave prognostic sign.

Electrocardiograms were not helpful in the evaluation of right heart pressure in these subjects except that minor P wave abnormalities were noted in all subjects with pulmonary hypertension at rest. However, abnormal P waves were also seen in subjects with relatively normal right heart pressures. There were a variety of electrocardiographic abnormalities noted which were difficult to interpret in terms of physiologic status. Even the electrical position of the heart was not consistent for the side of surgery. No significant electrocardiographic changes were noted in ten subjects during exercise or during oxygen breathing. It is of interest that despite the elevated pulmonary artery pressures and despite the clinical diagnosis of cor pulmonale in three cases, not a single electrocardiogram showed definite evidence of right ventricular hypertrophy. In general, our electrocardiographic findings are similar to those previously reported for the postpneumonectomy state [41-43].

Preoperative Evaluation. Preoperative studies have not been included in the present report for several reasons. In many instances such data are unavailable or limited in scope. In addition, pulmonary function tests are often distorted by the disease for which surgery is contemplated, making interpretation difficult. The diagnosis of

obstructive emphysema is particularly troublesome since expiratory slowing, abnormal distribution of gas, physiologic shunting, and even decreased diffusing capacity may occur on the basis of a pulmonary malignancy or granuloma. For this reason, physiologic studies limited to the "good lung" will prove of most value unless overall function is nearly normal. Since pulmonary perfusion has proved a major limitation in lung resection many thoracic surgeons have stressed the need for preoperative measurements of the pulmonary artery pressure, especially during occlusion of the pulmonary vessel to be transected [29,37,39,44,45]. A marked rise in pressure on occlusion of such a vessel must be taken as presumptive evidence of an insufficient remaining vascular bed.

It has been suggested that exercise during unilateral pulmonary artery occlusion will further define the limitation in perfusion function [29,45]. On the basis of available data, such a procedure must be expected to produce a significant pulmonary hypertension even in normal subjects if exercise is sufficient, and the degree of hypertension will be dependent on the increase in cardiac output resulting from exertion. Pulmonary artery pressures obtained under such circumstances must be correlated with simultaneous cardiac output determinations to be interpreted properly, and technical problems become considerable. However, by employing all available technics, most patients predisposed to a postoperative pulmonary insufficiency state should be discovered and resection may be limited or avoided to prevent the occasional unsatisfactory operative result.

SUMMARY

1. Clinical and physiologic observations in thirty-six postpneumonectomy patients have been presented. In the majority of cases there is a progressive overinflation of the remaining lung during the first postoperative year but no significant decrease in exercise tolerance. Pulmonary function tests and cardiac catheterization studies reveal a decrease in pulmonary diffusing capacity and an elevated right heart pressure on exertion. These responses are discussed and are believed to represent the expected pattern for a single normal remaining lung. There is no evidence of destructive changes in the remaining lung in most subjects, even after prolonged pulmonary overinflation.

2. Nine patients demonstrate more severe

respiratory symptoms. In four instances, these may be ascribed to a complicating cardiac or pulmonary disorder. The remaining five patients show evidence of chronic obstructive emphysema which is believed to have developed independent of, and, in four cases, prior to the pulmonary resection. The physiologic abnormalities in these patients are certainly aggravated as a result of the removal of functioning lung tissue.

3. Those patients with an abnormal remaining lung show resting pulmonary hypertension and, in a few instances, clinical evidence of cor pulmonale. The perfusion function of the lungs is particularly sensitive to pulmonary resection; preoperative tests applicable to this problem are discussed.

4. The effects of pneumonectomy on pulmonary artery pressure and pulmonary diffusing capacity are contrasted with the reported effects of exertion, both conditions resulting in an increased blood flow per unit of lung. An active vasomotor effect of exercise on pulmonary vasculature is believed to exist to explain the differences in response of the pulmonary vasculature to these two stimuli.

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Clinicopathologic Conference

Severe Abdominal Pain with Negative Physical and Laboratory Findings

S TENOGRAPHIC reports, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D. of weekly clinicopathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine, Preventive Medicine, and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

The patient was a thirty-five year old Negro laborer who was admitted to Barnes Hospital for the second time on May 1, 1959. He died on May 20, 1959.

The first admission to Barnes Hospital was from April 6, 1959 to April 27, 1959 and was for abdominal pain of one month's duration.

One month prior to admission the patient noted the onset of intermittent, transient episodes of diffuse, "griping," mid-abdominal pain, which tended to radiate bilaterally around to his back and occurred subsequently as frequently as every two to four hours throughout the day and night, without any apparent relationship to meals or to the patient's activity. The patient was aware only of the occasional association of a sensation of abdominal fullness with the pain; there was no nausea, vomiting, diarrhea, constipation, melena, fatty food intolerance, belching, or passage of flatus. The severity of the pain rapidly increased to the point that he was completely confined to bed, while the frequency of the pain made sleep impossible. Nothing was known which tended to relieve the abdominal pain. Two weeks prior to admission, the patient was admitted to another hospital where, after roentgenographic studies of the upper gastrointestinal tract and gallbladder were said to show "a few spots on the stomach." He was given some unknown medications with only transient, minimal relief of symptoms. After his discharge, he was very quickly incapacitated once more by the abdominal pain and was admitted to Barnes Hospital.

The patient had two episodes of "gonorrhea," about fifteen years before admission; he also had a gunshot wound in the right side of the groin in 1948, which did not require surgery and which

was followed up four years later by the "slug working its way out of the left buttock"; a "mild" high blood pressure was accidentally discovered in 1958; and there was "heavy" use of alcohol and cigarettes with frequent "binges." The patient's last medical evaluation was upon discharge from the U. S. Army and was said to have revealed no abnormalities. There was no allergic history nor had the patient had any fever or symptoms suggestive of cardiorespiratory, genitourinary or liver disease.

The findings on physical examination were as follows: the blood pressure was 180/110 mm. Hg, pulse 80, respirations 20, and temperature 37.3°c. The patient was an exceedingly muscular, Negro man, who appeared to be in no acute distress although he stated he had abdominal pain. The skin was warm and dry without any stigmas of chronic hepatic disease. The neck was supple and there was no venous distention or thyroid enlargement. The thorax was symmetrical and the lungs were clear to percussion and auscultation. The heart was not enlarged, the rhythm was regular, the tones were of good quality, and there was a grade 2 apical, highpitched, systolic murmur. The abdomen was flat, symmetrical, and soft with a palpable liver 1 to 2 cm. below the right costal margin. The extremities, back and spine were normal. The rectal examination was within normal limits as was the neurological examination.

The laboratory data revealed the following: The white blood cell count was 14,900/cu. mm. with 73 per cent segmented forms, 4 per cent stabs, 3 per cent eosinophils, 13 per cent lymphocytes and 7 per cent monocytes. The packed red cell volume was 40 per cent, hemoglobin 12.7 gm. per cent, sedimentation rate 37 mm./hour

uncorrected; the platelets appeared to be adequate in number but the red blood cell morphology was described as hypochromic on this and all subsequent examinations. On urinalysis, the urine specific gravity was 1.028, pH 5.0, with a trace of protein. On examination of the centrifuged urinary sediment there were 10 to 15 white blood cells per high power field. The blood cardiolipin reaction for syphilis was negative. The admission stool examination was negative for occult blood and neutral fat. The blood urea nitrogen was 8 mg. per cent, fasting blood sugar 68 mg. per cent, serum cholesterol 196 mg. per cent, amylase 80 units per cent, uric acid 1.6 mg. per cent, calcium 10.0 mg. per cent, phosphorus 3.8 mg. per cent, alkaline phosphatase 8.2 Bodansky units (repeat value was 7.6 Bodansky units), albumin 4.0 gm. per cent, globulin 2.5 gm. per cent, results of cephalin cholesterol flocculation test negative, thymol turbidity test 4.0 units, total bilirubin 0.8 mg. per cent. Serum glutamic oxaloacetic transaminase 18 units, and serum glutamic pyruvic transaminase 31 units. The bromsulfalein test showed 8.0 per cent retention of the dye, the "C" reactive protein reaction was 1 plus, and the antistreptolysin O titer was 25 units. Results of the bisulfite test for sickle cells were negative. A urine culture (clear voided specimen) revealed 8 colonies of white staphylococcus. Examination of the urine for Bence Jones protein, coproporphyrin (type III), and porphobilinogen (X 4) was negative. Examination of the stool for ova and parasites was negative on four occasions, while routine stool culture failed to reveal any pathogens. A single positive guaiac stool reaction was reported on the day prior to the performance of sigmoidoscopy. A first strength tuberculin skin test reaction was negative. The blood lead concentration (history of gun-shot wound) was 0.044 mg. lead in 100 gm. of blood. An electrocardiogram showed left ventricular enlargement with clockwise rotation. All roentgenographic examinations were reported as being within normal limits; these included a cardiac series, oral cholecystograms, upper and lower gastrointestinal series and excretory pyelograms. However, a review of these x-ray films disclosed the presence of multiple fragments of radio-opaque material in the soft tissue in the region of the left ischial tuberosity, with some irregularity of the bone (compatible with gun-shot wound, 1948).

During the initial period of hospitalization,

when the patient was undergoing various diagnostic procedures, his blood pressure ranged about 140 to 160/80 to 100 mm. Hg and subsequently tended to fluctuate around 145/90 mm. Hg. Although the patient remained afebrile during his entire hospitalization, he had a persistent leukocytosis with eosinophilia which was unaffected by a ten-day course of Achromycin® (1 gm.) administered daily. A liver biopsy revealed normal liver tissue. Sigmoidoscopy was non-revealing and a sternal bone marrow aspiration revealed cellular marrow with all elements normally adequate (impression: non-diagnostic). Bartropin, one tablet administered four times daily, had no noticeable effect on the abdominal pain which was almost continuous, nor did the addition of compazine reduce the requirements of analgesics which showed a definite increase after the first week of hospitalization. On the seventeenth hospital day, the patient was given "broad-spectrum" anthelminthic therapy (Delvex, 9 200 mg. administered three times daily). Four days later, the patient was free of all abdominal pain for the first time since onset of the present illness and, after a 72-hour period of being asymptomatic, the patient was discharged from the hospital with the diagnosis of "Helminthiasis, suspected" and given an additional five days' supply of Delvex.

The second admission to Barnes Hospital was from May 1, 1959 to May 20, 1959, and was occasioned by reappearance of abdominal pain. The patient denied anorexia, but stated that "he was afraid to eat because of pain" and that this had resulted in his losing 20 pounds of weight over the past two months. The pain was not relieved by any of the medications which were prescribed, but the patient related that it seemed to be better if he assumed a squatting position. The patient was readmitted for the purpose of exploratory laparotomy.

On physical examination the blood pressure was 170/110 mm. Hg., pulse 88, respirations 20, and temperature 36.8°c. The findings were identical to those on the first admission, except for the presence of very slight epigastric tenderness and the absence of a palpable liver on this examination.

Laboratory data revealed the following: The white blood cell count was 16,800/cu. mm. with 74 per cent segmented forms and 26 per cent lymphocytes. The hemoglobin was 13.1 gm. per cent. On admission two routine urinalyses

revealed the specific gravity to be 1.032 and 1.025, the pH was 5.0 and 4.0, the protein reaction was negative and 2 plus, sugar reactions negative, and the centrifuge urinary sediment showed 4-plus amorphous and calcium oxylate crystals on one occasion and 7 to 11 white blood cells on the other.

The patient underwent exploratory laparotomy on the second hospital day and died eighteen days later. During the last week of his life, the following blood studies were obtained: alkaline phosphatase 18.8 Bodansky units, calcium 11.0 mg. per cent, phosphorus 5.0 mg. per cent, amylase 229 units, results of cephalin cholesterol flocculation test negative, thymol turbidity test 3.0 units, total bilirubin 1.5 mg. per cent, sodium 137.0 mEq./L., potassium 6.7 mEq./L., carbon monoxide 25.4 mEq./L., chloride 93 mEq./L., and blood urea nitrogen 44 mg. per cent.

CLINICAL DISCUSSION

DR. EDWARD H. REINHARD: The case under consideration today deals with the problem of severe, recurrent abdominal pain in a young man. The fact that this pain was unassociated with any positive physical findings makes the diagnostic problem difficult. In addition, this case is different than usual in that although we are given the history, the physical findings, and the laboratory data, we are led by the resident who wrote the abstract of the case, to the door of the operating room, and no further. Let us begin our discussion then by looking at the roentgenograms.

Dr. Harvey A. Humphrey: Radiologic examinations of the chest, gallbladder, upper gastrointestinal tract, large intestine, and urinary tract were performed shortly after the patient's first admission to the hospital. Except for minimal left ventricular enlargement no significant abnormalities were detected. A few metallic fragments were evident in the left gluteal region.

DR. REINHARD: One of the causes of griping abdominal pain is certainly lead poisoning. This was considered in the differential diagnosis on this case on the first admission. A blood level was obtained which was normal. I think we can certainly assume, having followed the patient through his second hospital admission, that he did not have lead poisoning. However, I cannot refrain from commenting briefly on the history to the effect that the patient received a gunshot wound in the right side of the groin in 1948, the

slug working its way out through the left buttock four years later. Dr. Harrington, is there any evidence that a person can get lead poisoning by absorption of lead from bullets or lead shot in the soft tissue?

DR. WILLIAM HARRINGTON: Because of the relative frequency with which lead becomes implanted in the body in the form of shot, shrapnel, bullets, etc., and the rarity of clinical evidences of lead poisoning attributable to this source, the possibility of lead intoxication from bullets lodged in the tissues has been questioned.* However there are isolated instances wherein serum and urinary lead levels in the toxic range have been observed associated with symptoms compatible with lead poisoning, relieved by surgical removal of the lead-containing foreign bodies.† It would seem, therefore, that lead absorption from implanted bullets may be a cause, however rare, of lead poisoning.

Although some of the features of the fatal illness of the patient under discussion are compatible with lead poisoning, this is an improbable diagnosis despite the apparent presence of a potential source of intoxication. I would be very unwilling to favor this diagnosis over other more

likely possibilities.

DR. REINHARD: Dr. Gieselman, this patient was suspect of having helminthiasis and was treated with Delvex. Four days later he was free of all abdominal pain for the first time since the onset of his illness. He was discharged from the hospital with the diagnosis of "helminthiasis suspected." Does helminthiasis ever produce this much pain and are there any other parasitic infections that produce a syndrome that is compatible with this patient's symptomatology?

DR. RALPH GIESELMAN: My answer would be no to both questions. I think that the degree and severity of the abdominal symptomatology here would be most unusual for any type of parasitic infestation. The fact that there was some temporary improvement with a so-called broad-spectrum anthelminthic drug, should not lead us to the assumption that symptomatology was due to this cause. The worms that are affected by this drug generally produce little or no abdominal pain.

* Aub, J. C., Fairhall, L. T., Minot, A. S. and Reznikoff, T. Lead Poisoning. Medicine Monographs, vol. 7. Baltimore, 1926. Williams & Wilkins Co.

† Machle, W. Lead absorption from bullets lodged in tissues. Report of two cases. J. A. M. A., 115: 1536–1541, 1940.

DR. REINHARD: Dr. Shatz, would you comment on any gastrointestinal lesions that might give severe, constant pain with almost com-

pletely negative physical findings.

DR. BURTON SHATZ: There are several diseases terminating fatally that could fall in this category. The most common is carcinoma of the body or tail of the pancreas. In this situation a patient has a great deal of upper abdominal pain radiating to the back, which may be aggravated by eating and may be relieved by sitting up. This patient felt better in a squatting position. I have never heard this described in connection with pancreatic disease, but it may be relevant. The negative physical and radiologic findings in this seriously ill man further suggest carcinoma of the pancreas as a good possibility. Impairment of the mesenteric circulation is a second condition that must be considered in the presence of abdominal pain with few physical findings and has been referred to in recent literature as "abdominal angina." This is caused by arteriosclerotic changes in the mesenteric arteries which diminish the flow of blood to the intestines. The pain that results is thought to be a result of ischemia as also occurs in angina pectoris and intermittent claudication. This is a very difficult and dangerous diagnosis to make. It usually occurs in older people who complain of abdominal pain without any positive physical or roentgenographic findings and, therefore, the diagnosis is made only after everything else is excluded. In this particular patient, his youth and the absence of any evidence of arteriosclerosis in other organs is very much against the diagnosis of abdominal angina. Now this patient had a moderately enlarged liver and an elevated alkaline phosphatase. He had no jaundice, so that the usual explanation for the elevated alkaline phosphatase such as obstruction of the common duct cannot be used here. This makes one think of infiltrative disease of the liver. Therefore, metastatic carcinoma or granuloma of the liver should also be considered. Of this group, carcinoid can give abdominal pain, hypertension, and an enlarged liver with an elevated alkaline phosphatase. He had a grade 2 systolic murmur of the heart but from the description this was probably due to left sided valvular disease rather than right, which is what one would expect in carcinoid. I believe that of these three I would favor carcinoma of the body or tail of the pancreas in this case.

DR. REINHARD: Dr. Lonergan, would you like to express a preference for any of these or for any other diagnosis?

Dr. Warren Lonergan: I believe we should consider the diagnosis of diffuse vascular disease. The patient did have hypertension transiently; periodically he had albumin in the urine and cellular elements; there was only one elevation of temperature mentioned and that was minimal. He did have a mild eosinophilia; there was a rising leukocytosis; hence I would wonder whether this man might not have had polyarteritis nodosa.

DR. REINHARD: In other words intestinal angina might develop as a result of an occlusion of the mesenteric artery secondary to periarteritis. These are interesting suggestions. Dr. Massie, should we mention dissecting aneurysm?

DR. EDWARD MASSIE: This was not the pain of dissecting aneurysm and I did not seriously consider that diagnosis. I would propose another diagnosis which is mesenteric thrombosis, perhaps associated with arterial emboli. I do not know the source of the emboli, but we do have a patient who has vascular disease with hypertension and left ventricular enlargement; the systolic murmur is undoubtedly associated with the left ventricular enlargement. There is no arrhythmia, but mesenteric embolus would be more common than mesenteric vascular atherosclerotic occlusion, in view of the age of the patient.

DR. REINHARD: Dr. Parker, would you discuss the concept of intestinal angina? What is this syndrome and to what extent can it be likened

to angina pectoris?

DR. BRENT PARKER: This syndrome should really be called intermittent mesenteric ischemia. I think it is quite similar in mechanism to angina pectoris. Intestinal blood flow when the intestines are at rest is adequate, but when the intestines are active, following eating, flow is inadequate because it cannot be increased due to vascular changes. Pain then develops. This, of course, is similar to what occurs in angina pectoris when the patient feels pain on exertion. In addition, this syndrome is ordinarily seen in older people and is associated with atherosclerotic disease. Dunphy found that seven of twelve patients who died of acute mesenteric thrombosis or embolism had had pain characteristic of intestinal angina before the acute catastrophic event occurred.

DR. REINHARD: There is an excellent editorial

on intestinal angina in Lancet* for June 1958. This editorial emphasized the fact that the pain does not always come on immediately after meals. The pain is usually exaggerated after meals; however, there may be a free interval. The pain may get much worse an hour or an hour and a half after the meal, reaching its peak intensity two or three hours later rather than immediately after the meal. In angina pectoris, of course, the cause of the pain is the extra work load on the heart caused by exertion, whereas in intestinal angina, the load on the intestine that causes the pain is the increased work resulting from the meal.

In view of this discussion, I believe it is pertinent to know exactly what the relationship of this patient's pain to meals was. Why did he refuse to eat? Did he really have an exacerbation of pain after eating? Dr. Binder, you saw this patient clinically. I wonder if you could give us

any information.

DR. MORTON BINDER: He was a very vigorous, muscular man. For ten years prior to the onset of his illness, he had been a heavy drinker. He refrained from eating because this seemed to aggravate his pain. However this pain developed at any time and was not always related to eating. Demerol® never completely relieved his pain. Whenever I walked into this man's room he was holding his abdomen with his hands and more often than not was squatting in a chair, or in the corner. This was the position of maximum comfort.

DR. REINHARD: I quote from the editorial in Lancet. "The patient who nibbles at his food during the day and takes substantial meals in the evening will suffer from nocturnal attacks." Did that apply to this patient? Did he eat his big meal at night?

DR. BINDER: As far as I know he never ate a big meal subsequent to his first visit to my office.

DR. PARKER: We might note that Bean in his review of a case of abdominal angina published in 1957, commented that his patient was much relieved of his pain by sitting up and leaning forward. He felt that this was effective in relieving the drag on the intestines and so decreased the pain. Perhaps a similar mechanism explains the squatting noted in the present patient.

DR. REINHARD: Did this patient have mesenteric arterioocclusion?

DR. PARKER: Yes, it was proved at autopsy.

DR. REINHARD: Dr. Butcher, do patients who have intestinal angina due to postprandial ischemia of the intestines always have mesenteric vascular occlusion, or may they have arteriosclerotic narrowing without complete thrombotic occlusion? Is there anything comparable to what we see with angina pectoris, the pain being brought on by exertion in the absence of actual thrombotic occlusion?

Dr. Harvey Butcher: I do not think it is necessary to have complete organic occlusion of the superior mesenteric artery in order for this syndrome to develop. Some of the reported cases have had some small channels still present.

DR. Reinhard: It seems to be well established that intestinal angina may occur in association with severe cardiac decompensation. Ende* has reported six such cases. Furthermore, several authors*† have reported patients with chronic hepatic disease with or without cardiac failure who had intestinal angina, and yet at postmortem examination did not have any actual organic occlusion; there was always narrowing of some sort, but not complete organic occlusion.

We might comment very briefly on the differentiation between arterial and venous mesenteric thrombosis. Dr. Bradley, how do you distinguish

between these two?

Dr. Richard Bradley: Patients who have sudden arterial occlusion will in general have more severe symptoms. They will have fewer abdominal findings in the way of distention and more sudden and rapid onset of the disease. Those with venous occlusion of the bowel will in general have more in the way of abdominal findings, i.e., tenderness, distention, etc.

DR. REINHARD: It was commonly thought at one time that mesenteric arterial occlusion always produces rapidly progressive pain leading to shock and death ensuing within a matter of a few days, unless the condition can be relieved surgically. Dr. Butcher, is this concept correct, or can chronic pain result from arterial mesenteric thrombosis?

DR. BUTCHER: Patients can live quite a long time with mesenteric arterial occlusion. They may not necessarily have symptoms. The occlusion that produces the symptoms is the one

^{*} Intestinal angina (editorial). Lancet, 1: 1211, 1958.

^{*} Ende, N. Infarction of the bowel in cardiac failure. New England J. Med., 258: 879, 1958.

[†] Johnson, C. C. and Baggenstoss, A. H. Mesenteric vascular occlusion. II. Study of 60 cases of occlusion of arteries, and of 12 cases of occlusion of both arteries and veins. *Proc. Staff Meet. Mayo Clin.*, 24: 649, 1949.

that develops relatively rapidly. How rapidly it has to develop to produce necrosis or how progressive it has to be to maintain chronic symptoms, I do not know. However, at autopsy there are patients with complete occlusion of the mesenteric artery with viable intestine and without previous symptoms.

DR. Reinhard: Dr. Parker has already mentioned the report by Dunphy* of twelve patients with fatal occlusion of the mesenteric artery, seven of whom had abdominal pain preceding the attack by considerable periods of time. Do you have anything to add, Dr. Bradley?

DR. BRADLEY: It has been reported that the intestine can be deprived of its blood supply in experimental animals in such a way as to produce this deprivation over a three-month period. During this time collateral flow develops in the animals. In addition, acute obliteration of blood supply in a 14 cm. length of intestine can be produced without any symptoms in the experimental animals.

Dr. Reinhard: I also found a report by Laufman† on the experimental production of gradual slow occlusion of the superior mesenteric artery in dogs. This investigator was able to produce ultimate complete occlusion in three out of six dogs. In the animals with complete occlusion a low grade enteritis developed with erosion of the villi and leukocytic infiltration in the mucosa and the submucosa. These animals lost weight and appeared ill, but actual infarction developed, and they survived. Apparently in human subjects, mesenteric arterial thrombosis usually goes on to infarction with very acute symptoms but I believe there is also evidence that a more chronic syndrome can occur. Certainly this was true in the cases that Dunphy reported. Dr. Shatz?

DR. SHATZ: We saw a similar patient in this hospital a few years ago. This patient had a roentgenographic picture indistinguishable from regional enteritis as a result of the occlusion of the mesenteric artery supplying that segment of small bowel. In this patient, of course, the obstruction had been going on for a long period of time, so that chronic occlusion certainly occurred.

Dr. Reinhard: I believe this situation is entirely comparable to the experiments in dogs.

DR. SHATZ: Yes. I think it is worth mentioning that this diagnosis of abdominal angina is a wonderful diagnosis for gastroenterologists. It makes it possible for them to make a diagnosis in elderly people who have abdominal pain of recent onset without any roentgenographic or physical findings. In the younger age group we have the functional diseases to fall back on. In the older age group we now can call this abdominal angina. But I would like to re-emphasize that this is a very dangerous diagnosis to make because a good percentage of these people will end up with carcinoma or some other serious organic disease.

DR. REINHARD: I agree with Dr. Shatz. I believe we are on dangerous grounds in making a definitive diagnosis of arterial mesenteric thrombosis in this patient.

Jenson and Smith* have published an excellent clinical study of fifty-one cases of mesenteric infarction seen at the University of Minnesota Hospitals. These authors emphasize that there are two clinical syndromes associated with mesenteric vascular occlusion; in one there is a sudden complete occlusion of a major mesenteric artery, and in the other there is gradual occlusion of the artery or veins. The incidence of various symptoms and physical signs in these different syndromes is presented in this article. If the patient we are considering today had a mesenteric vascular occlusion at all, it would certainly fall into the latter group where the occlusion occurs slowly.

Dr. Shatz, would you expect the transaminase level to be elevated if the patient had had infarction of the bowel?

DR. Shatz: While one would theoretically expect the serum transaminase to be elevated in bowel necrosis, this is usually not the case.

DR. REINHARD: In making the diagnosis of mesenteric vascular occlusion with infarction of the intestine, we are in real trouble in another regard and that is (the point has already been repeatedly commented on), why should a thrombosis develop in the patient? This patient was only thirty-five years old and it is difficult to believe that he had marked arteriosclerosis. However, young people can have localized plaques in the coronary arteries producing coronary occlusion. It certainly is possible that the same thing could happen in the mesenteric artery. Dr. Butcher, I believe that when this

^{*} Jenson, C. B. and Smith, G. A. A clinical study of 51 cases of mesenteric infarction. Surgery, 40: 930, 1956.

^{*} Dunphy, J. E. and Whitfield, R. D. Mesenteric vascular disease. Am. J. Surg., 47: 632, 1940.

[†] LAUFMAN, H. Gradual occlusion of the mesenteric vessels. Surgery, 13: 406, 1943.

FEBRUARY, 1960

does occur the arteriosclerotic plaques are almost always in the first few centimeters of the mesenteric artery, at the root of the artery. Is that correct?

DR. BUTCHER: That is correct.

DR. REINHARD: This patient was found to have mild hypertension one year prior to his admission to Barnes Hospital. If he had severe hypertension this would have been supportive evidence in favor of this diagnosis, but as far as we know he had only minimal

hypertension.

I would like to comment on Jenson and Smith's study again. They analyzed the diseases associated with mesenteric vascular occlusion in their fifty-one cases. Twenty-five of these patients had arteriosclerotic or hypertension disease of the heart without cardiac decompensation, and six had heart failure. One patient had subacute bacterial endocarditis, and one had periarteritis nodosa. Thus thirty-three of the fifty-one patients had some form of cardiovascular disease. In ten of the fifty-one patients mesenteric vascular occlusion developed following abdominal surgery. Two of the patients had had recent infarctions: one had polycythemia vera, one had congenital hemolytic icterus, two had diabetes, one had pancreatitis, and one had cancer of the pancreas.

Most of these conditions can be excluded in the case we are discussing today. It is interesting to speculate on the outside possibility that the patient might have had both a carcinoma of the pancreas as suggested by Dr. Shatz and an occlusion of the superior mesenteric artery.

I presume that carcinoma of other organs might occasionally also lead to this. It is apparently established that carcinoma of other organs in addition to the pancreas leads to an increased incidence of thrombosis. On the other hand, I have to admit if he had carcinoma of the head of the pancreas when he was taken to the operating room the first time there isn't any terribly good reason to make a second diagnosis. Dr. Shatz, is severe, constant, unrelenting pain unusual in carcinoma of the pancreas?

DR. SHATZ: No.

Dr. Reinhard: Are you not bothered by the finding of exacerbation after eating?

Dr. Shatz: The relationship here is so vague and indefinite.

DR. REINHARD: Dr. Gieselman, do you have anything to add? Do you believe the patient had mesenteric arterial occlusion?

DR. GIESELMAN: That would not be my first choice.

DR. REINHARD: I was going to ask you which of these secondary causes might have contributed to the development of mesenteric thrombosis, but I guess it is not fair to ask you this if you are confident that the patient did not have a vascular occlusion.

DR. Massie: Dr. Reinhard, I would like to suggest that this patient's hypertension was not so minimal and was not of such short duration. The electrocardiogram showed evidence of left ventricular enlargement. People with hypertension do not have left ventricular enlargement on the tracing without cardiac enlargement. If patients with hypertension have electrical evidence of cardiac enlargement, then we would assume that hypertension has been present for a long time, and has been significant.

DR. REINHARD: The diagnosis of arterial occlusion of the mesenteric artery is rather attractive to me as has become apparent by this discussion, and I am grasping at straws for support for this diagnosis. I must say however that the evidence for severe vascular disease of any sort is mighty slim here. Dr. Gieselman?

DR. GIESELMAN: One thing that disturbs me in this diagnosis is explaining the borderline bromsulfalein test and the elevated alkaline phosphatase which rose progressively during the hospital stay. These findings suggest some type of disease involving the liver such as a metastatic process or less likely a granulomatous process.

DR. REINHARD: The alkaline phosphatase rose to 18 terminally, but we have no idea of what happened to the patient in the meantime.

DR. GIESELMAN: It was elevated slightly at the time of his admission.

DR. REINHARD: It was between 7 and 8 Bodansky units, that's true.

Dr. Shank, do you have any comments on the reported cases of mesenteric arterial thrombosis in association with chronic hepatic disease or cirrhosis? Do you have any suggestion as to what the mechanism might be? Is there an etiological relationship between these two? There haven't been enough cases to permit one to say there is an etiological relationship, but there have been some cases reported.

DR. ROBERT E. SHANK: I am afraid I cannot make any pertinent comment.

DR. REINHARD: I would like to comment on this patient's weight loss. I believe that the obvious explanation is that he lost weight be-



Fig. 1. Endarterectomy specimen showing a portion of the internal elastic lamella at the top. Verhoeff-Van Gieson stain \times 5.

cause he was not eating. On the other hand, I might point out that it has been reported in recent years that if occlusion of the mesenteric artery is gradual and collateral circulation is sufficient to prevent frank necrosis, the patient may be left with a chronic bowel syndrome, at times with stricture or ulceration, and this may produce the malabsorption syndrome. As a matter of fact, Shaw and Maynard* suggest that this diagnosis should be considered in patients with an unexplained malabsorption syndrome and that thromboendarterectomy may represent an effective therapy for the malabsorption syndrome due to this particular mechanism. As has been brought out by this discussion, I have made the diagnosis of mesenteric artery thrombosis, although there are potent arguments against it. If the autopsy reveals superior mesenteric artery thrombosis, the patient probably had some primary disease to which this was secondary. This could be an arteriosclerotic plaque at the origin of the mesenteric artery. As Dr. Massie suggested he might have had more hypertension in the past than the history would indicate. He certainly could have had a carcinoma of the pancreas, with or without an associated mesenteric vascular occlusion.

Dr. James Walsh will now present the findings at surgery and will summarize briefly the postoperative course.

DR. JAMES WALSH: On the second hospital

day the patient underwent exploratory laparotomy, appendectomy, and node and muscle biopsy, with the postoperative diagnosis being abdominal pain, unknown etiology. It was mentioned at the time of operation that the superior mesenteric pulse, and I quote "seemed to be weak, but bowel adequately supplied with blood." Following the operation the patient's abdominal pain reappeared with the same severity as before and finally necessitated reexploration on the nineteenth hospital day. At that time no preoperative diagnosis was made; however, the patient underwent a celiac and superior mesenteric endarterectomy, with the postoperative diagnosis being occlusion of the celiac and superior mesenteric arteries. This was considered to be due to arteriosclerotic plaques. The bowel color was said to be good on completion of the operation. However, the patient never regained his normal status and the vital signs deteriorated very rapidly. On the twentieth hospital day another abdominal exploration was performed and resection of the distal two-thirds of the small bowel and the right colon was undertaken. At this time the area was gangrenous, although it was said that the remaining part of the intestine appeared to be viable. The patient died two hours post-operatively. Dr. Saltzstein will discuss the surgical pathology.

DR. SIDNEY SALTZSTEIN: The first specimen that we received was a needle biopsy specimen from the liver which, as the protocol states, showed essentially normal liver. The specimen from the first exploration on May 2 consisted of a lymph node, some muscle and the appendix.

^{*} Shaw, R. S. and Maynard, E. P., III. Acute and chronic thrombosis of the mesenteric arteries associated with malabsorption: a report of 2 cases successfully treated by thromboendarterectomy. *New England J. Med.*, 258: 874, 1958.

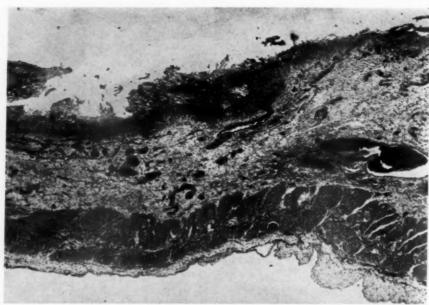


Fig. 2. Ileum showing mucosal necrosis, extreme vascular congestion, and histologically normal muscle. Hematoxylin and eosin X 40.

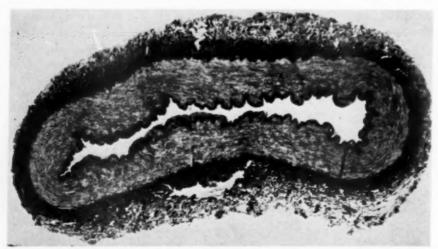


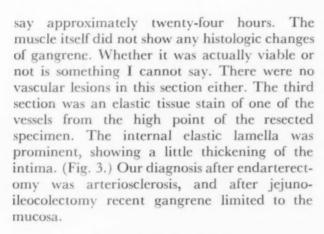
Fig. 3. Artery at high point of jejunoileocolectomy. There is minimal intimal thickening. Verhoeff-Van Gieson stain \times 50.

We could not establish any diagnosis from these specimens. There certainly was no evidence of periarteritis nodosa or any similar lesion. The third specimen that we received, which was on May 19, was that obtained during endarterectomy. This grossly consisted of a few pieces of soft tissue which were yellow in color and rubbery in consistency. The largest measured 1.3 by ½ cm. A section of this material showed rather loose fibrous tissue. There were some cholesterol clefts. A few areas here and there showed either a persistent lumen or an attempt at recanalization. Portions of the internal elastic lamella at one edge were visable so the lesion lay in the intima. The lesion was interpreted as an organized

thrombus. (Fig. 1.) The last specimen, which we received on the following day, was as Dr. Walsh described, the right colon and two-thirds of the small intestine. In almost the entire specimen the serosal surface appeared intensely congested, dusky, and purple red. On opening the bowel, the entire mucosa of both the small intestine and the colon was hemorrhagic. No actual ulcerations of the mucosa were detected. There were no thromboses, but the veins and arteries were packed with blood. The mucosa of the small intestine through the whole length of the specimen was acutely inflammed and necrotic. (Fig. 2.) If I had to make an estimate of how long this process was going on, I would



Fig. 4. Diffuse myocardial fibrosis, minimal nature, was found scattered in a few regions of the heart. Hematoxylin and eosin \times 150.



PATHOLOGIC DISCUSSION

DR. W. STANLEY HARTROFT: When the remainder of the patient's body was autopsied we were impressed with his muscularity and extreme physical development. He was not obese. Incisions and drainage tubes were present but will not be described. The heart was externally normal, but a little large (500 gm.). Microscopically (Fig. 4) diffuse fibrosis was present here and there in the neighborhood of the vessels. The valves were completely normal and all chambers completely free of antemortem thrombi. The heart of this physically powerful man, although admittedly enlarged, was not as disproportionately increased in size as the absolute weight would indicate, owing to his impressive muscular development. Hypertrophy was limited to the left ventricle, reflecting his moderate degree of hypertension.

The lungs were heavy, weighing 1,600 gm. and both the larger vessels and septal capillaries were congested. (Fig. 5.) Blood had extravasated

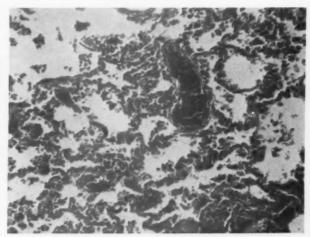


Fig. 5. Arteries, veins and capillaries throughout the lungs of this patient were exceedingly congested. Stasis on the arterial side was particularly prominent (upper right). Hematoxylin and eosin × 150.

into some of the alveoli. But thromboses, infarction or any other interference with the pulmonic vasculature had not developed.

The aorta, coronary arteries, and the abdominal vessels were of considerable interest in view of his history. The degree of coronary arteriosclerosis was not great. One would not expect it to be great in a man of only thirty-five years of age, and particularly in a man of this race, Negro. The degree of arteriosclerosis in the aorta was recorded as only moderate. Thrombi were found in both the superior and inferior mesenteric vessels. The origin of the superior mesenteric artery was occluded by both recently formed and older thrombi. The older of the two was white and organized; it could have formed during the initial period of his history two and a half months before death. An elastic tissue stain of a section of the superior mesenteric artery (Fig. 6) revealed only a slight arteriosclerosis. Present also in the section was a recent thrombus of only twenty-four to forty-eight hours' duration. In the inferior mesenteric artery (Fig. 7) another recently formed thrombus was found overlying an intima thickened only slightly. The bowel remaining at autopsy was normal but for a recent fibrosanguineous coating over the serosal surface, sterile on culture, of the type commonly seen following operations such as this man had undergone. Sanguineous fluid, 200 ml., were found in the peritoneal cavity.

There were infarcts in various organs. In the adrenal gland, they involved its cortex and several cortical nodules which were present. (Fig. 8.) The infarcts were about forty-eight

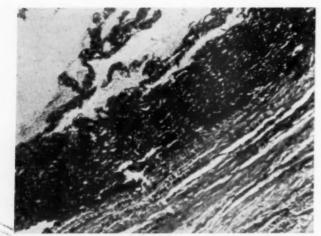


Fig. 6. Only minimal arteriosclerosis could be demonstrated in sections of this inferior mesenteric artery. Elastic tissue appears black; the lumen of the vessel is at the upper left. Vierhoef-van Gieson stain × 150.



Fig. 7. A portion of a recent thrombus (upper left) was found completely occluding and overlying an only slightly thickened intima of the inferior mesenteric artery. Hematoxylin and eosin \times 150.

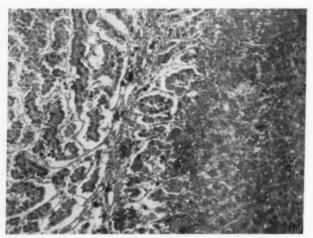


Fig. 8. Infarcts of recent origin in the adrenal involved several cortical nodules (benign adenoma). The necrotic nodule is shown at the right. Hematoxylin and eosin \times 150.

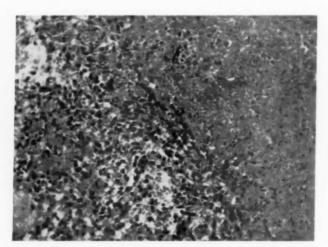


Fig. 9. Recent infarcts (upper right) were also found in the spleen. Hematoxylin and eosin \times 250.

hours old. Another infarct (Fig. 9) of about the same age was found in the spleen. Older infarcts were present in both kidneys, and in them a few glomeruli and tubular remnants had survived. These infarcts could have developed at the very beginning of his illness. Afferent arterioles of the glomeruli were hyalinized, reflecting his hypertension. Most of the hyalinization had involved glomerular roots and juxtaglomerular cells. (Fig. 10.) The macula densae were unusually prominent in these kidneys. Glomeruli were larger and more cellular than usual.

The liver was of interest, despite the fact that the biopsy specimen, taken seventeen days before his death, was completely normal. Grossly it

was mottled by yellowish and hyperemic zones, giving it a "geographic" appearance. Many regions (Fig. 11) were necrotic, the necrosis being of less than twenty-four or thirty-six hours' duration. Thrombi were found in many branches of the hepatic artery, visible not only microscopically (Fig. 12) but also grossly. Seas of necrosis lapped the shores of islands of surviving parenchyma around portal triads. (Fig. 13.) Only periportal haloes of intact liver cells were present. The bile duct epithelium, however, was completely normal, showing that in man as well as in animals the branches of the hepatic artery are not the nutrient arteries of bile duct mucosa, because the latter is able to survive perfectly in the presence of complete occlusion of the hepatic arterial blood supply. Arterial blood is however absolutely necessary for survival of hepatic

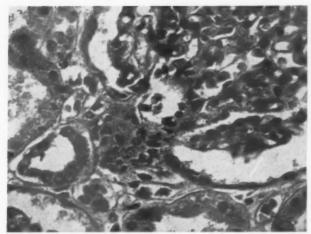


Fig. 10. Hyalinization of the juxtaglomerular cells at the arterial roots of the glomeruli were frequently encountered. The macula densa (below and to the left of the glomerulus) was hypercellular and prominent. Hematoxylin and eosin × 150.

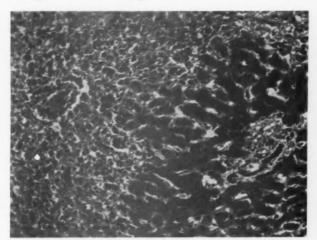


Fig. 11. Throughout nearly the entire liver, variable degrees of pericentral necrosis of recent origin were found (left) with, by way of contrast, well preserved periportal cells (right). Hematoxylin and eosin \times 150.

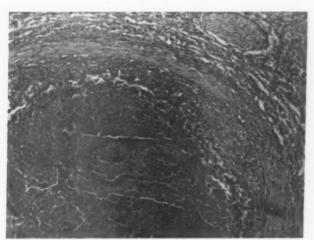


Fig. 12. Recently formed thrombi were found in many of the large branches of the hepatic artery with only early stages of organization near the intima as shown here. Hematoxylin and eosin \times 150.

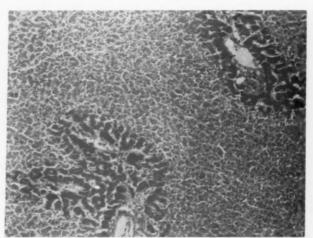


Fig. 13. In the most severely necrotic areas of the liver the appearance was dramatically altered by seas of necrosis which appeared to lap the shores of periportal islands of preserved parenchyma. Hematoxylin and eosin × 150

parenchyma. In other areas the necrosis took a more extreme form than that illustrated and extended right up to portal triads and from lobule to lobule.

The autopsy findings did not establish the nature of this man's disease as well as the surgical specimens; the principle diagnosis is without doubt mesenteric arterial occlusion. The occlusion was equally without doubt, thrombosis not embolism, because thorough search failed to reveal any reasonable source for embolism. None of the rare diseases of the arterial system that we think of, such as periarteritis nodosa could account for the formation of thrombi. In my opinion the arteriosclerosis was not of sufficient

severity to explain the thromboses. Therefore I prefer to call it agnogenic, or idiopathic multiple arterial thromboses of unknown origin. Of course, I am not so sure that multiple arterial thrombi, non-occlusive in type, are as rare as we believe, because some of us believe they may be involved in the pathogenesis of atheromatous plaques. The older part of the thrombus found at the origin of the mesenteric artery from the aorta fits in perfectly with the clinical discussion we have had suggesting a partial occlusion for quite some time before the final complete occlusion by a second thrombus precipitated the catastrophic event leading to bowel resection.

The older thrombus was probably present when the surgeon with his sensitive fingers, seventeen days before death, sensed a weaker than normal

pulse.

The final anatomic diagnoses were multiple arterial thrombi of unknown etiology: marked narrowing of the orifice of the superior mesenteric artery by an organized thrombus, recent thrombi in superior and inferior mesenteric arteries, multiple thrombi in small hepatic arteries with multiple large recent infarcts of the liver, extensive central necrosis of the liver, recent and depigmented infarct of spleen, old infarcts (three) of kidneys, recent depigmented infarct in adrenal cortex; severe congestion of the intestine and colon; a partially healed, 30 cm. incisional wound on the midline of the abdomen (history of endoarterectomy of superior mesenteric and

celiac artery performed May 19, 1959); surgical absence of ileum, cecum and a part of ascending colon with end-to-end anastomosis of jejunum to colon; (history of resection of gangrenous intestine performed May 20, 1959); fibrinopurulent peritonitis; fibrinosanguineous peritoneal effusion, 270 ml.; extensive intra-alveolar hemorrhage of the lungs, 1,630 gm.; mucous material in trachea and bronchi; bilateral pleural effusion, 50 ml. in each space; and marked congestion and uric acid infarcts in the kidneys. The accessory diagnoses were arteriosclerosis of aorta and coronary arteries, moderate; hypertrophy and dilatation of the heart (500 gm.); focal fibrous thickening of epicardium; cholesterolosis of gallbladder; and advanced fibrous thickening of parietal pleura over diaphragms and thoracic wall.

Primary Aldosteronism*

A Case with Severe Hypertension

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I N 1955 Conn described a clinical syndrome characterized by episodic muscular weakness, intermittent tetany, paraesthesias, polyuria and polydipsia, hypertension and hypokalaemic, hypernatraemic alkalosis [1-3]. His description was based on a patient in whom he considered the syndrome arose from an adrenal disorder and he termed the condition primary aldosteronism. An adrenal adenoma was found at operation and dramatic improvement occurred after its removal. Since then, several further examples of this condition have been found, the adrenals in each case being the site of hyperplasia or a benign or malignant tumour

We describe here another case of primary aldosteronism in which symptoms were present for at least five years before removal of an adrenal adenoma. The most striking clinical finding was severe hypertension which had been treated by thoracolumbar sympathectomy and ganglion-blocking drugs. Causes of secondary hypertension are now known to be numerous, and errors in diagnosis will be reduced only by awareness of uncommon syndromes such as that of primary aldosteronism.

METHODS

The general procedure of metabolic balance studies as described by Albright and Reifenstein [12] was followed. The patient was given an average diet with no added salt. Duplicates of the twenty-four hour diet were analysed on four occasions during the balance, the results being given in Table 1.

Plasma sodium and potassium were estimated by flame photometry, chloride by the method of Van

Slyke [13], plasma alkali reserve by the method of Van Slyke and Cullen [14], plasma magnesium by the method of Orange and Rhein [15], blood urea and urea clearance by King's technic [16]. Urine ammonia estimations according to King [16] were obtained on completion of twenty-four-hour specimens collected

TABLE I ANALYSES OF FOUR DUPLICATIONS OF THE TWENTY-FOUR-HOUR DIET

Constituent	Amount Found by Analysis				
Potassium (mEq./day)	71.3	70.5	73.1	76.1	
Sodium (mEq./day)	118	116	114	119	
Chloride (mEq./day).	120	120	121	122	
Phosphorus (mg./day)	1,130	1,160	1,210	1,190	
Calcium (mg./day)	076	695	716	752	
Nitrogen (gm./day)	13.7	14.0	14.0	14.7	

in bottles containing acetic acid as preservative, and stored in the refrigerator. Calcium in the serum, food, faeces and urine was estimated by the method of Tisdall [17], urinary and faecal phosphorus by the method of Briggs [18] and nitrogen by the method of Koch and McMeekin [19]. The serum inorganic phosphorus and alkaline phosphatase were estimated by the method of King [16] and faecal fat by a modification of King's method [16]. The combined inulin and para-amino hippuric acid clearance were determined by the method of Goldring and Chasis [20]. Urinary excretion of aldosterone, cortisol and corticosterone were measured at the Middlesex Hospital by the physiochemical method of Ayres et al. [21]. Estimations of 17-ketosteroids and 17-hydroxycorticosteroids were by the method of Norymberski, Stubbs and West [22].

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Fig. 1. Presacral pneumogram showing an oval shadow lying above the depressed left kidney.

CASE REPORT

In June 1951, the patient (C. B.), a thirty-eight year old man, experienced difficulty for the first time in lifting his feet off the ground. This episode lasted some four hours. During December 1951, and again three months later, he felt pain in both calves for about four days, occurring together with unsteadiness of gait. During the second of these attacks he was admitted to the hospital where his blood pressure was found to be 200/120 mm. Hg. No retinopathy was detected. There was tenderness in both calves. He was thought to have thrombosis of the deep veins in the legs and therapy with Tromexan® was started. Soon after bed rest the pain ceased and has not since returned. His blood urea was found to be 24 mg. per cent and an intravenous pyelogram revealed no abnormalities. His urine contained a trace of protein, occasional red cells and hyaline casts. An electrocardiogram showed marked ST depression in standard leads I and II with biphasic T waves. A sodium amytal sedation test resulted in a fall in blood pressure from 200/160 mm. Hg to 120/90 mm. Hg. Although he was symptomless, thoracolumbar sympathectomy was performed in two stages in April and May 1952.

Twenty-four hours after the first stage operation the patient experienced very great thirst, had difficulty in producing saliva and became troubled by nocturia. In addition he began to have attacks of generalised weakness, each lasting two to four days

and occurring at least once weekly. In a typical attack, which might start at any time of the day, but most frequently in the morning, he observed that all his limbs were weak. His walking was unsteady with foot drop, and he had difficulty in shaving, dressing and writing. Between attacks his physical power was normal. Postoperatively, he attended the outpatient department and readings of his blood pressure suggested that the sympathectomy had had little effect on his hypertension, figures of 200/140 mm. Hg being frequently recorded. The patient continued to complain of thirst, nocturia and episodic weakness. He was referred to St. George's Hospital and admitted for the first time in February 1955. His general condition was good and there was no evidence of weakness at that time. There was clubbing of the fingers, which he himself had first noticed in 1950. His blood pressure was 240/140 mm. Hg. There was no clinical evidence of left ventricular enlargement and the fundi showed only slight irregularity of the lumen of the arterioles. The urine contained a trace of protein, a few leukocytes, scanty red cells and granular casts. An intravenous pyelogram revealed no abnormalities and results of a phentolamine test were negative. A regimen of Ansolysen® and reserpine, administered orally, was begun and the patient was discharged. Later, during an outpatient visit, he was seen during an attack of generalised paresis. A diagnosis of primary aldosteronism was considered and his plasma potassium was found to be 2.0 mEq./L. and plasma bicarbonate 39 mEq./L. He was readmitted for presacral pneumography which showed that the left kidney was depressed and an oval shadow was visible above. (Fig. 1.)

The patient was transferred for further study to the Metabolic Unit, Royal National Orthopaedic Hospital, Stanmore. In July 1956 an adrenal cortical adenoma was removed from the left adrenal gland, together with half of the remaining gland. A renal biopsy specimen was also obtained. The patient made an uneventful recovery and since then has been well, with no nocturia, episodic weakness or excessive thirst. Eighteen months after removal of the tumour his blood pressure was recorded as 180/110 mm. Hg.

INVESTIGATIONS

The pre- and postoperative blood biochemical findings are given in Table II.

Studies of Renal Function. The patient was first noted to have minimal proteinuria in 1952 and this was a persistent finding when we started treating him in 1956. Postoperatively the minimal proteinuria was still present six months later, but had disappeared by March 1958.

Preoperatively the urine specific gravity did not exceed 1.010. Urine dilution was unimpaired, the lowest urine specific gravity being 1.002, and the whole test load was excreted within four hours. Identical results were obtained twenty-three days after

Table II
PRE- AND POSTOPERATIVE BIOCHEMICAL FINDINGS

Data	Initial* Values	Post- operative Values
Serum potassium (mEq./L.)	2.2-3.0	4.7
Serum chloride (mEq./L.)	93-100	98-104
Serum sodium (mEq./L.)	137-147	133-146
Plasma alkali reserve (mEq./L.)	33.5-39.2	24.2-28.2
Serum magnesium (mg./100 ml.)	1.9-2.2	
Serum phosphate (mg./100 ml.)	2.4-3.5	3.8
Serum calcium (mg./100 ml.)	8.2-10.3	8.0
Blood urea (mg./100 ml.)	27-44	33
Serum proteins (gm./100 ml.)	6.8	7.6
Serum albumin/globulin	1.3	0.9
Thymol turbidity	0.6	
Serum alkaline phosphatase (King-Armstrong units/		
100 ml.)	7.2	6.9
Glucose tolerance test	Normal	

^{*} Before potassium supplementation.

operation. Three months after operation his urine could be concentrated up to 1.020; the urine was again diluted to specific gravity 1.002 but only three-quarters of the test load was excreted within four hours.

In order to test the capacity for urine acidification, a total of 561 mEq. of ammonium chloride was given over a three-day period. The urine pH dropped only from 6.9 to 6.6.

The combined inulin clearance and Tm_{PAH} was determined during the control period by the method advocated by Goldring and Chasis [20]. Because the infusion caused severe abdominal pain, only three-quarters of the priming dose was given, and the infusion was maintained at three-quarters of the advocated rate. With this same modification, the test was repeated six months after removal of the tumour. The results are shown in Table III.

The potassium clearance at different times during the balance study is shown in Table IV, calculated from the average daily urinary potassium during any one three-day period, and a single serum potassium determination during that period.

Salivary and Faecal Electrolyte Excretion. Salivary electrolyte concentrations were measured in relation to the rate of salivary flow, which was varied by chewing paraffin wax at different speeds of mastication according to the method used by Garrod et al. [23]. The results of pre- and postoperative electrolyte measurements at comparable rates of salivary flow (about 0.6 ml./minute) showed that removal of the aldosterone-secreting tumour was associated with an approximate doubling of the Na/K ratio (from about 0.10-0.13 to 0.23-0.25). At the same time there was

Table III

UREA AND INULIN CLEARANCES AND Tm PAH

00	70	46
49		
		49

Note: Values given are averages of measurements over two consecutive periods (sixty minutes in the case of urea, and thirty minutes in the case of inulin and paraamino hippuric acid).

an approximate fivefold increase in the faecal Na/K ratio from the preoperative value. Both these findings are in general agreement with the observations of Milne, Muehrcke and Aird [11], and similar salivary electrolyte changes were noted by Chalmers and associates [6].

Electrocardiographic Findings. Preoperatively, when the serum potassium was 2 mEq./L., there was considerable ST depression in all standard leads, aVL, aVF and $V_{5,7}$, and there were prominent U waves. SV_{2,3} were deep. The changes indicated the presence of left ventricular hypertrophy as well as hypokalaemia. Postoperatively, when the serum potassium was normal, there was persistent T wave inversion in II, III, aVF and V_7 , with slight ST depression. The electrical axis was vertical. These abnormalities were thought to be the result of the left ventricular hypertrophy. (Figs. 2A and B.)

Adrenal Hormone Studies. During preliminary investigations the urinary excretions of 17-ketosteroids and 17-hydroxycorticosteroids were measured and found to be normal (9 mg. and 7.5 mg./twenty-four hours, respectively). Special steroid estimations were

TABLE IV
POTASSIUM CLEARANCE

Period	Urine Potassium (mEq./ 24 hr.)	Serum Potassium (mEq./L.)	Potassium Clearance (ml./min.)
Period 1 (control).	60	2.4	17
Period 8 (after NH ₄ Cl)	24	2.4	7
Period 14 (after KCl)	180	5.2	24
Period 21 (post- operatively)	59	5.6	7.1

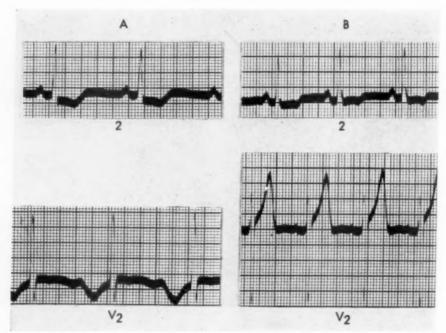


Fig. 2. Electrocardiogram: Standard lead II and V_2 . A, preoperatively when the plasma potassium was 2 mEq./L. B, three months after operation when the plasma potassium was normal.

then obtained at the Middlesex Hospital by Mr. Ayres, Dr. O. Garrod, Mrs. P. A. Simpson and Dr. J. F. Tait, who reported that the urinary excretions of aldosterone, cortisol (hydrocortisone) and corticosterone were measured by a physiochemical method (Ayres et al. [21]). Table v shows the values obtained in this patient (1) on a normal potassium intake (72 mEq./day), (2) after four days on a high potassium intake (172 mEq./day), the patient having retained 274 mEq. of potassium, and (3) five days after removal of the adrenal tumour, on 72 mEq. of

Table V
ALDOSTERONE, CORTISOL AND CORTICOSTERONE
ESTIMATIONS

	Observed Values			
Steroids	Normal Intake of Potassium	High Intake of Potassium	5 Days Post- operatively	
Potassium intake				
(mEq./day)	72	172	72	
Serum potassium				
(mEq./L.)	2.6	4.0	5.1	
Aldosterone (µg./	33	28.4	0.84	
Cortisol (µg./day)	20.8	16.4	11.0	
Corticosterone				
(μg./day)	0.8			

potassium/day. The sodium intake (117 mEq./day) was constant throughout.

Steroid production by the adrenal tumour and by the portion of the left adrenal gland resected at operation was also measured. The tissues were placed in an ice-cooled thermos flask immediately after removal. The measurements were made three hours later by incubating slices of the tissue according to a method previously described by Ayres and associates [21]. The tumour slices produced relatively large amounts of aldosterone, some cortisol, but little corticosterone, whereas slices from various parts of the left adrenal gland yielded only traces of aldosterone and appreciable amounts of cortisol and corticosterone, although some of these slices contained areas of tissue histologically similar to that of the tumour.

Histopathology. The report on the pathology of the tumour removed at operation disclosed that the specimen weighed 4 gm. Microscopic examination showed the tumour to be well circumscribed, although no capsule was present. There was abundant lipoid material present, some of which was birefringent. The tumour consisted of cells which showed a moderate degree of variation in shape and size. The nuclei were large and showed prominent nucleoli; mitotic figures were, however, infrequent. The features were those of an adenoma of the adrenal cortex. There was no evidence of malignancy.

A renal biopsy taken at the time of operation was sent to Dr. Darmady who reported that the section showed a small fragment of kidney tissue. The capsule seemed thickened and there were scattered areas of round cell infiltration under the capsule. Many of the

glomeruli were replaced by fibrous nodules; one showed a well marked crescent. The proximal tubules were distorted in places and the epithelium flattened. There was no vacuolation. In some areas there was eosinophil material lying within the lumen of the tubules. The loops of Henle were not observed. Some arterioles were thickened. The appearances were those of nephrosclerosis with hypertension.

Metabolic Balance Studies. After base-line values had been obtained and renal function tests performed. there followed six weeks of metabolic balance studies, when the effects of ammonium chloride and added dietary potassium were studied. The tumour was then removed and the balance was continued for three weeks postoperatively. The patient was readmitted for biochemical estimations three months and six months after operation. The main results of the balance study are shown in Figure 3. In the first eighteen days of balance studies the patient received no treatment or dietary supplement. The balance was then quite normal except for a slight retention of sodium and chloride. There was no clear loss or retention of potassium. Since the serum potassium at this time was 2.4 mEq./L. while the urine potassium remained at normal levels, namely 60 mEq./day, the potassium clearance (17 ml./minute) was abnormally high. The urinary ammonia during these eighteen days averaged 70 mEq./day, which is a high normal value. In the initial period, then, the balance for potassium, sodium, chloride, phosphorus, calcium and nitrogen was essentially normal in spite of the hypokalaemic alkalosis and high urinary ammonia production. From the nineteenth to twenty-first day inclusive the patient was given ammonium chloride, 10 gm. daily (187 mEq./day orally). This caused an immediate drop in the alkali reserve and increase in urinary ammonia production. The alkali reserve fell to 18.2 mEq./L. on the second day of administration of ammonium chloride, returning to the level of 30 mEq./L. on the fourth day after stopping the drug. The urinary ammonia began to increase on the second day, reached levels of 140 mEq./day on the two days after stopping the drug, and gradually returned to previous levels by the sixth day after stopping it. The arterial blood pH measured on the third day of administration of ammonium chloride was 7.45 compared with 7.50 previously. A severe attack of muscle paresis developed on this day.

From the twenty-eighth to the thirty-eighth day (periods 10 to 13) the patient was given a supplement (100 mEq./day) of potassium chloride orally, divided into three doses. This dosage was increased to 170 mEq./day from the thirty-eighth to the forty-second day, when the balance study was discontinued for the four days prior to operation, although the patient continued to take 170 mEq./day up to the day before operation. The ingestion of potassium chloride quickly corrected the hypokalaemic alkalosis, the serum potassium rising to 4 mEq./L. on the third day

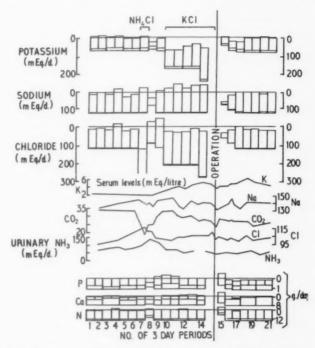


Fig. 3. Serum values of potassium, sodium, bicarbonate and chloride, and balance of potassium, sodium, chloride, phosphorus, calcium and nitrogen. Ammonium chloride was given in period 7 and potassium chloride from period 10 until operation. Faecal and urinary outputs are plotted upwards from the intake.

of treatment and reaching levels of 5 mEq./L. after twelve days, while the alkali reserve dropped to 28 mEq./L. and the urinary ammonia fell to the normal level of 50 mEq./day. The serum chloride remained within normal limits throughout potassium chloride therapy. The potassium chloride supplement produced a marked positive balance for potassium and chloride and a negative sodium balance. The retention of potassium gradually declined, urinary potassium increasing, until the addition of further administration of 70 mEq./day of potassium chloride. This resulted in an increase in potassium retention although the urinary potassium was still rising when the balance study was discontinued. The total retention of potassium during the fifteen days included in the balance studies amounted to 740 mEq. with a possible further retention of 200 mEq. during the four days not followed. The retention of chloride in these fifteen days was 420 mEq. and the total loss of sodium 515 mEq., so that there was a net gain of 195 mEq. of the acid radical in excess of base. From five days after the commencement of the potassium supplement until the time of operation the serum chemistry was normal. Following operation (periods 16 and 17) there was the usual postoperative balance for potassium, sodium and chloride, but by the seventh day after operation, when the patient was eating a normal diet without added supplement, the balance for these elements was essentially normal. The

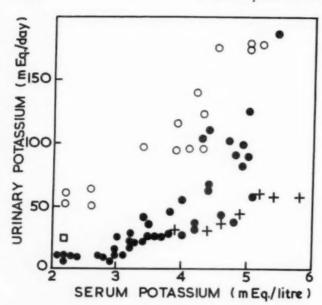


Fig. 4. Daily urine excretion of potassium plotted against serum potassium. Key: • = Subjects with normal kidneys. 0 = Patient preoperatively. + = Patient post-operatively. = Patient after administration of ammonium chloride.

blood values at this stage were as follows: serum potassium 5.4 mEq./L., chloride $102 \, \mathrm{mEq./L.}$, sodium $140 \, \mathrm{mEq./L.}$, and the plasma alkali reserve $26.8 \, \mathrm{mEq./L.}$

There was no significant loss or retention of calcium, phosphorus or nitrogen during the period of study, although the urinary excretion of calcium and phosphorus increased during potassium repletion, and lowered after the operation. Milne, Muehrcke and Aird [11] noted positive postoperative calcium and phosphorus balances associated with nitrogen loss.

COMMENTS

The Renal Excretion of Potassium. In Figure 4 the daily excretion of potassium, calculated from three-day urine collections, is plotted against the corresponding level of serum potassium during control, ammonium chloride, potassium supplement and postoperative periods. On the same graph are values for twentyfour-hour urine potassium, similarly plotted against corresponding serum levels, from subjects with normal kidneys; these values are taken from Mahler and Stanbury [24], and they include results from experimental potassium depletion, and one case of potassium deficiency of alimentary origin. The graph emphasises (1) the high urinary potassium excretion of our patient at abnormally low plasma levels during the control period, and during potassium supplement periods when plasma levels were normal; (2) the lowering of the urine potassium excretion

for a single three-day lag (Fig. 3) as a result of the acidosis induced with ammonium chloride, and (3) the effect of removal of the aldosteronesecreting tumour in bringing potassium excretion into the normal, and possibly low normal range, for the corresponding serum level.

The potassium clearance depends on the load, that is, the potassium intake. This is shown very clearly, for example, by the balance study carried out by Evans and Milne [25] on a normal healthy man. With a normal intake of potassium, a serum potassium of 4 mEq./L. and a urine output of approximately 60 mEq./day the potassium clearance was 10 ml./minute. On the addition of 200 mEq./day of potassium the potassium balance very rapidly reached equilibrium, and the normal kidney preserved complete homeostasis. The serum potassium was now 4.4 mEq./L., the urine potassium approximately 250 mEq./day and the clearance approximately 40 ml./minute. In our patient the potassium clearance on a normal intake of potassium was 17 ml./minute. When 170 mEq./ day were added the potassium clearance was 24 ml./minute. Thus, although our patient had a high potassium clearance on a normal potassium intake, during the fifteen days on the potassium chloride supplement (when he was in strongly positive potassium balance, and had already reached a normal serum potassium level), his potassium clearance was lower than that of a normal person with the same intake but higher than that of a potassium-depleted subject with normal kidneys. The high excretion of potassium in the urine of our patient at such low plasma levels is a feature of all published cases of primary aldosteronism in which urine and serum values have been determined. It has been stated that patients with primary aldosteronism are resistant to the replacement of the potassium deficit by oral supplement [1,2,7]. We did not find this to be true in our patient and there are now several reports of proved cases of primary aldosteronism in which supplementation effected a retention of potassium and raised the plasma potassium to normal [4-6,9]. On the other hand, the patient of Evans and Milne [25], who subsequently proved to have primary aldosteronism, retained potassium on supplementation but the serum potassium did not rise above 2.8 mEq./L. [11]. Oral ammonium chloride had a delayed effect on urine potassium, which was reduced by about half for three days after stopping the administration of ammonium

Date (1956)	Supplement	Plasma CO ₂ Com- bining Power (mEq./ L.)	Serum Potas- sium (mEq./ L.)	Urine Potas- sium (mEq./ day)	Potas- sium Balance (mEq./ day)
30/5	None	33.5	2.5	63	-4
12/6	None	33.1	2.2	52	+7
15/6	Ammonium chloride	21.2	2.1	60	-3
16/6	Ammonium chloride	18.2	2.2	24	+19
17/6	None	24.2	2.2	24	+19
18/6	None	24.3	2.2	24	+19
20/6	None	29.6	2.6	49	+6
22/6	100 mEq./day KCl	34.2	3.4	96	+64
25/6	100 mEq./day KCl	33.2	3.9	95	+65
27/6	100 mEq./day KCl	31.4	4.3	95	+65
29/6	100 mEq./day KCl	29.2	3.9	116	+42
2/7	100 mEq./day KCl	30.2	4.2	141	+29
4/7	170 mEq./day KCl				
	170 mEq./day KCl	27.5	5.0	179	+48
6/7	170 mEq./day KCl	28.4	5.2	179	+48
12/7*	None	24.2	3.9	30	-6
13/7*	None	28.2	4.4	30	-6
16/7*	None	26.8	4.5	37	+18
17/7*	None	27.6	4.9	43	+20
18/7*	None	27.2	4.9	43	+20
20/7*	None	26.8	5.2	59	+5
23/7*	None	26.3	5.8	57	+7
25/7*	None	24.2	5.4	57	+7
1/8*	None	26.1	5.2	59	+4

^{*} Postoperatively

chloride. During these three days the potassium intake was reduced by 14 mEq./day but the potassium balance was plus 19 mEq./day and, therefore, there must have been some retention of potassium during this period. (Table vi.) Table vi shows also that there was some positive correlation between the plasma CO2 combining power and the urine potassium during the control and ammonium chloride periods, the acidosis lowering the urine potassium. Any such inter-relation during the periods of potassium supplement will have been masked by high potassium excretion consequent upon high intake. It seems from Figure 4 that the postoperative potassium excretion in our patient was on the low side of normal for corresponding blood levels. The patient, however, was not having extra potassium after operation whereas the normal values on the graph were obtained from subjects having in some cases 100 to 150 mEq./day. The full balance data show (Fig. 3) that during the postoperative period the patient was in positive potassium balance, retaining 144 mEq. in twenty days while his plasma levels were above the normal range. The evidence therefore suggests that postoperatively potassium retention was abnormally high. In general agreement with this is the finding of Chalmers,

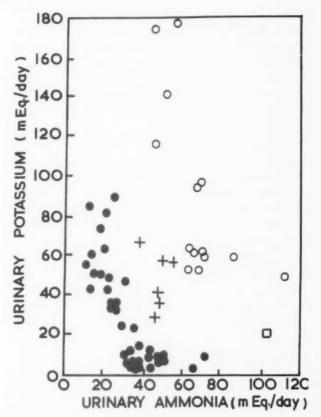


Fig. 5. Relationship between daily urinary excretions of ammonia and potassium. Key: 0 = Patient preoperatively. + = Patient postoperatively. = Patient when acidotic. = Values from cases of chronic potassium depletion of alimentary origin. (Schwartz and Relman [27].)

Fitzgerald, James and Scarborough [6] in their patient with primary aldosteronism, that post-operatively the plasma potassium rose to 6.5 mEq./L. without potassium supplement and as high as 8.5 mEq./L. with supplement. During the postoperative period of thirty days, their patient retained 610 mEq. of potassium.

The Renal Excretion of Ammonia. Normal persons excrete 30 to 50 mEq./day of ammonia [26]. During the control period our patient excreted 60 to 70 mEq./day, which is abnormally high. Ingestion of ammonium chloride caused a rise in the excretion of ammonia which reached its peak about four days after stopping the intake of salt. The addition to the diet of 100 and then 170 mEq./day potassium chloride caused a gradual decline in urinary ammonia to a level which was maintained after operation. Of interest is the reciprocal relationship between urinary ammonia and urinary potassium shown in Figure 5. Also plotted for comparison are values taken from Schwartz and Relman [27] who described potassium repletion in two

patients suffering from chronic potassium depletion of alimentary origin; these values also show a reciprocal relationship between urinary potassium and urinary ammonia. It is obvious that both ions are excreted in much greater amounts by our patient than by the patients of Schwartz and Relman. The significance of this finding will be discussed subsequently.

Recurrent Muscle Paresis. Since the serum potassium had been falling gradually during the preceding four weeks, and was at its lowest recorded value of 2.2 mEq./L. at the time, the attack observed during the administration of ammonium chloride may have been due simply to the effects of slow potassium changes rather than to the acute effects of ammonium chloride. However, a similar attack associated with administration of this salt was described by Earle et al. [28] in a possible case of primary aldosteronism. In this case, as in ours, ammonium chloride reduced the alkali reserve but had no effect on the serum potassium level, a finding also described in proved cases of primary aldosteronism by Crane, Vogel and Richland [7] and Eales and Linder [9]. Sartorius, Roemmelt and Pitts [29] point out that when ammonium chloride is given to a normal subject, despite the increased excretion of potassium on a constant intake, the plasma potassium is maintained or even raised, indicating the release of intracellular stores of potassium. Intracellular loss of potassium in acidosis has been demonstrated also by Elkinton and associates [30]. Moore, as reported on by Crane, Vogel and Richland [7], produced hypokalaemic alkalosis experimentally by gastric suction, and showed that the plasma potassium was restored by administration of ammonium chloride. Clarke and associates [31] also noted an increase in serum potassium from 3.5 mEq./L. to 4.0 mEq./L. on administration of ammonium chloride to the experimentally depleted normal subject and, since urinary loss continued, the potassium must have been drawn from intracellular stores. The absence of this response in primary aldosteronism is probably due to the severity of potassium depletion. Evidence is presented elsewhere in this paper that in our patient the potassium-depleted cells contained an increased amount of sodium, and that the latter ion was released, presumably in exchange for hydrogen ions, during the administration of ammonium chloride. This exchange may have been a factor in the development of the paresis.

Sodium Balance. Even when measured as

averages of three-day collections, the urinary sodium values before operation fluctuated considerably. During this eighteen-day period the patient retained 111 mEq. of sodium. (The corresponding net potassium balance for this period was zero.) Corresponding plasma values were within normal limits except for one value of 147 mEq./L. A sodium balance control period, comparable in length with ours, is available only in the case of Mader and Iseri [4] who found a marked positive balance accompanied by serum sodium values which were usually high and a negative potassium balance. High serum values before potassium repletion are described in most of the published cases of primary aldosteronism. During the three days when ammonium chloride was given the sodium balance was negative, but scarcely more so than during control period number 4. In the three days immediately following ammonium chloride, when the intake of sodium was reduced by 51 mEq./day, the balance was markedly positive, as was the potassium balance during this period. During the administration of potassium chloride the sodium balance became negative as the potassium balance became positive. The reciprocal relationship between sodium and potassium balance during potassium repletion of potassium-depleted subjects is a further feature of the cases of primary aldosteronism already referred to, and was noted by Mahler and Stanbury [24] in potassium-losing renal disease, by Schwartz and Relman [27] in alimentary potassium depletion, and by Black and Milne [32] in experimental potassium depletion. The immediate effect of operation on the sodium balance was to make it positive, as would be expected, and later the balance became normal.

Cation Shifts. Cumulative changes in the amounts of intracellular sodium and potassium (Fig. 6) were calculated as described by Elkinton and Danowski [33]. The initial extracellular fluid (ECF) volume was assumed to be 20 per cent of the patient's body weight; potassium changes were corrected for changes associated with protein metabolism. Such calculations were based on the assumption that chloride neither enters nor leaves the cells and hence that changes in extracellular fluid volume can be calculated from plasma chloride and chloride balance measurements.

Reliable balance data were not available from our patient for a few days around the date of operation, and for calculations of postoperative

changes the assumption had to be made that the ECF volume did not change during this period. The starting point of postoperative changes is therefore open to error, but calculations of ion shifts beyond this point are unaffected by any error in this assumption.

The preoperative results show: (1) an increase in ECF volume of nearly $4\frac{1}{2}$ L., (2) a net gain of intracellular potassium of 767 mEq. out of 829 mEq. retained by the patient during this period, and (3) a net loss of intracellular sodium of 1,141 mEq., 716 mEq. of which stayed in the expanded ECF and 425 mEq. of which were excreted. These changes are shown in Figure 6 with corresponding plasma levels and plasma alkali reserve.

The increase of ECF volume of 4.5 L. in our patient, before operation, is very similar to that reported by Mahler and Stanbury [24] in their description of the potassium repletion of a case of potassium-losing renal disease. Mader and Iseri [4] reported an increase of about 1 L. during treatment with potassium in a patient with primary aldosteronism. A similar increase was reported by Elkinton, Squires and Crossley [34] in cases of metabolic alkalosis due to chronic potassium deficiency and also by Schwartz and Relman [27] during the potassium repletion of chronic potassium deficiency of alimentary origin.

The Relationship of the Potassium Deficiency to the Alkalosis. It seems safe to conclude that during the preoperative potassium repletion period in our patient more sodium was lost from the cells than potassium was gained. The inference from this finding is that before treatment the patient had lost a certain amount of potassium from his cells and a greater quantity of sodium had entered. Balance data on the two cases of Milne, Muehrcke and Aird [11] indicate intracellular changes similar to those reported here, but Chalmers et al. [6] and Mader and Iseri [4] found that of the intracellular potassium lost, only about three-fourths and two-thirds, respectively, were replaced by sodium.

In acute experimental potassium depletion in rats [35] and in man [32] potassium lost from cells was only partly replaced by sodium and it was inferred in these studies that part of the potassium deficit was balanced by movement of hydrogen ions from the ECF into the cells, thus giving rise to ECF alkalosis and low urinary ammonia and acidity. This concept was strengthened by the finding that potassium

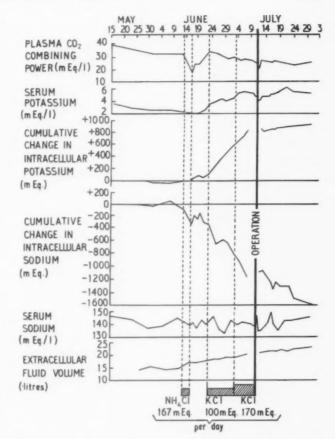


Fig. 6. Serum potassium, sodium and plasma CO₂ combining power, cumulative changes in intracellular potassium and sodium, and changes in extracellular fluid volume.

repletion abolished the alkalosis and led to an increase in urinary ammonia and acidity, due presumably to displacement of intracellular hydrogen ions by potassium.

The alkalosis in our patient, however, could not have been due to ion exchange between cells and ECF since the calculated cation shifts showed that intracellular potassium depletion was more than balanced by sodium alone. Also, in contrast to the observations in acute experimental potassium deficiency, the urinary ammonia excretion in our patient was high during potassium depletion (also noted by Milne, Muehrcke and Aird [11] and Eales and Linder [9]) and was gradually lowered during repletion, urinary potassium increasing with decreasing ammonia excretion. A similar relation between the daily excretions of these two urinary ions was noted by Schwartz and Relman [27] in chronic potassium deficiency and can be interpreted by the concept of Berliner, Kennedy and Orloff [36] which postulates renal tubular secretion of potassium and hydrogen ions in exchange for reabsorbed sodium ions. Ammonium ion excretion is an index of hydrogen ion excretion, the latter decreasing as more potassium ions become avail-

able for exchange.

The potassium depletion described by Schwartz and Relman [27] was due to alimentary loss, and in their patients the sparing action of one ion on the other was sufficient to restrict potassium excretion to very low levels at the expense of increased hydrogen ion excretion (as ammonium ion). In our patient, however, both potassium and ammonium ion excretion were excessively high (Fig. 5), an observation in agreement with that of Eales and Linder [9] and Milne, Muehrcke and Aird [11]. Excessive excretion of these ions could occur as a result of increased reabsorption of sodium, thus giving rise simultaneously to potassium depletion and alkalosis. There is abundant evidence that aldosterone promotes such reabsorption. Hypersecretion has been demonstrated in many conditions associated with sodium retention, e.g., nephrosis, congestive heart failure and hepatic cirrhosis [37]. Much of the evidence reviewed by Garrod, Simpson and Tait [38,39] relates aldosterone secretion to sodium and water retention. If aldosterone excess caused potassium depletion and extracellular alkalosis by the mechanism suggested, the cells might become depleted of both potassium and hydrogen, and this would allow more sodium to enter than potassium to come out. This situation would account for the intracellular cation changes seen in our patient on potassium repletion.

Sodium balance data and plasma sodium values from our own and from other cases, as previously presented, provide further evidence for sodium retention during untreated primary

aldosteronism.

Renal Function. The abnormally low glomerular filtration rate (Cl_{In}) and maximal tubular excretory capacity (Tm_{PAH}) were probably due to the nephrosclerosis. The further reduction in glomerular filtration rate three months after operation, indicated by the urea clearance value (Table III), is a feature of many published cases of primary aldosteronism. In those of Chalmers, FitzGerald, James and Scarborough [6], Eales and Linder [9], and Milne, Muehrcke and Aird [11] the lowered filtration rate coincided with a postoperative fall in blood pressure, but in our patient there was no marked relief of the hypertension after removal of the tumour. In one of three cases of

primary aldosteronism briefly described by Dustan, Corcoran and Page [40] there was a similar fall in glomerular filtration rate not due to a fall in blood pressure.

Aldosterone Estimations. Dr. Garrod provided the following comments on the results of the estimations: "The moderately raised preoperative excretion of aldosterone is in keeping with our own and other worker's findings in cases of Conn's syndrome. The extremely low urinary excretion of aldosterone after removal of the tumour, compared with the proportionately much smaller fall in cortisol excretion agrees with our findings in the case reported by Chalmers, FitzGerald, James and Scarborough [6], and indicates that aldosterone excretion by the non-tumourous tissue was being suppressed. This interpretation is supported by the incubation studies on the tissue removed at operation and agrees with the hypothesis which we have previously put forward (Garrod, Simpson and Tait [39]). It would seem that this suppression may not be easily reversible, for it was still present three months after operation in the case reported by Chalmers et al., and in the present case the aldosterone excretion did not rise after partial potassium repletion."

CLINICAL COMMENTS

Clinically, this patient resembled other cases previously described, apart from the fact that his hypertension was more severe than in most and that he did not, to the best of our knowledge, exhibit tetany. In 1951, when he had what was probably the first of his attacks of muscular weakness, his hypertension was considerable although labile, and in the absence of relevant symptoms, retinopathy or evidence of progressive renal damage he underwent bilateral thoracolumbar sympathectomy. Assessment of the effect of this operation on his blood pressure is difficult but certainly readings of 240 to 210 systolic and 150 to 130 mm. Hg diastolic were commonly recorded during his visits from 1952 to 1956, and beneficial therapeutic action is scarcely clear. After removal of the adrenocortical tumour the hypertension, although reduced, was still present and in March 1958 his blood pressure varied between 180 to 110 mm. Hg when lying down and 160 to 105 mm. Hg when standing. The lability may be to some extent the result of sympathectomy. The reason for the persistence of the hypertension remains unknown, although an obvious but unproved

hypothesis is that it is the result of renal damage secondary to prolonged hypertension or hypokalaemia or both.

It will be noted that thirst and polyuria were experienced for the first time shortly after the first stage thoracolumbar sympathectomy in 1951, attacks of muscular weakness becoming frequent thereafter. Garcia Llaurado [41] demonstrated that there is an increased excretion in urine of an electrolyte-regulating corticoid in the immediate postoperative period and Garcia Llaurado, Neher and Wettstein [42] isolated the hormone and identified it as aldosterone. Garcia Llaurado and Woodruff [43] suggest that postoperative aldosteronism may result from either increased production of aldosterone or impairment of the capacity of the liver to inactivate the hormone. It is possible that one of these mechanisms may have been responsible for precipitating our patient's symptoms after the sympathectomy.

The initial diagnosis of our case was made on the basis of the history, hypertension, the presence of hypokalemic alkalosis and the demonstration of an adrenal tumour radiologically. While in the fully developed case raising the possibility of primary aldosteronism may depend only on awareness of the existence of the syndrome, the problem of diagnosis in some cases may be one of great difficulty. Milne's second subject was a woman complaining only of transient occipital headache who was found to have hypertension. An electrocardiogram suggested the presence of hypokalaemia and later she was found to have an adrenocortical tumour. The electrocardiogram which is often performed routinely on new patients with hypertension may thus be of great value.

The differential diagnosis from primary renal disease with hypokalaemic alkalosis (as opposed to the more common acidosis) may again be a formidable problem, as pointed out by Milne, Muehrcke and Aird [17], apparent distinguishing characteristics being possibly fallacious. Hyperplasia or a tumour of the adrenals may not be shown by air insufflation and the salivary Na/K ratio may be affected by secondary aldosteronism. Bilateral surgical exploration may have to be the last investigation before primary aldosteronism is excluded.

SUMMARY

A case of primary aldosteronism is described. The presenting features were some indefinite FEBRUARY, 1960

unsteadiness of gait, with incidental hypertension discovered on routine examination. Symptoms of polyuria, polydipsia and attacks of generalised weakness did not develop until ten months later, shortly after a thoracolumbar sympathectomy had been performed for the hypertension.

After a diagnosis of primary aldosteronism had been made, balance studies were performed over a period of seven weeks preoperatively and three weeks postoperatively. The biochemical findings are discussed.

At operation an aldosterone-secreting tumour was removed from the left suprarenal gland.

Except for the persistence of (a less marked) hypertension the patient has remained normal for the twenty-four months since the operation.

Acknowledgment: The patient was under the care of Dr. J. F. Dow at St. George's Hospital and Drs. R. Nassim and P. G. Walker at the Metabolic Unit, Royal National Orthopaedic Hospital, Stanmore, and we are indebted to them for their help and permission to report this case. We are grateful to Mr. Ayres, Drs. O. Garrod, J. F. Tait and Mrs. P. A. Simpson for the steroid estimations at the Middlesex Hospital, and to Dr. V. Wynn for blood pH determinations. Dr. Darmady kindly studied the renal biopsy and Dr. Dexter reported on the pathology of the tumour tissue. Lastly, we should like to thank the subject of this report for his patience and cooperation.

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Multiple Myeloma Manifested as a Problem in the Diagnosis of Pulmonary Disease

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PULMONARY involvement in multiple myeloma is uncommon. In a series of fifty-seven cases reported by Kenny and Moloney [7], there were no symptoms or physical findings referable to the respiratory tract. Extraskeletal involvement is most often present in the liver, spleen and lymph nodes [2,3].

In the case to be presented, extraosseous pleuropulmonary involvement was a dominant feature.

CASE REPORT

A sixty year old white, married woman complained of weakness, anorexia, dyspnea and pain in the left lower side of the chest anteriorly.

Her past medical history included a subtotal hysterectomy and right salpingo-oophorectomy performed in 1943 for fibroid tumors of the uterus. In 1949, hemorrhoidectomy was performed. In 1953 she had undergone subtotal thyroidectomy for a benign nodule. There were no symptoms of thyrotoxicosis. In 1955 she was treated at home for pneumonitis. Every few months thereafter she was bedridden for a few days to a week with fever, cough and pains in the chest.

System review revealed no significant symptoms not related to her present illness. A roentgenogram of her chest taken at a mobile chest survey unit twenty-four months before admission was reported as normal.

The patient's present illness began insidiously fifteen months before admission, when she noted pain in her left iliac area. Her family physician, in another city, discovered a mass in the left iliac area. She was thought to have diverticulitis, and was found to be anemic. She received several transfusions of whole blood, but continued to lose weight, felt weak, and pain persisted. Eight months after the onset of these symptoms she underwent an exploratory laparotomy. A cystic mass measuring 3.5 by 3 by 1 cm. in diameter was found adherent to the rectum and was removed. The pathological report was a benign Gartner's duct cyst.

Following this operation her symptoms of weakness persisted. Dyspnea developed as well as sternal pain and pain in the left anterior portion of the chest; she

remained anorectic and continued to lose weight. Pain in her right hip and knee developed. During the several weeks before admission her dyspnea had increased and nausea and vomiting developed.

She was first seen by one of us (E. A. F.) in December 1957, approximately fifteen months after the onset of her present illness. Physical examination at this time revealed a fairly well developed, thin, white woman, approximately sixty years of age, who appeared to be extremely weak and chronically ill. The temperature was 98.5°F., pulse 88 per minute, respirations 26 per minute, and blood pressure 152/84 mm. Hg. Examination of the head and neck was essentially within normal limits. Small, tender nodes were palpable in both axillas. On percussion, there was dullness in the lower half of the left side of the thorax. On auscultation, the breath sounds were normal on the right side but decreased to absent in the lower third and mid-third anteriorly and posteriorly. A few rales were heard at the right base. The heart sounds were normal. There was normal sinus rhythm. The second aortic sound was louder than the second pulmonic. No murmurs were heard. The apex beat could neither be seen nor felt. The abdomen did not appear to be distended. An operative scar was present in the left iliac region. The liver was palpable 3 inches below the right costal margin; the spleen was palpated 2 inches below the left costal margin. There was moderate tenderness in the right upper quadrant of the abdomen. Pelvic examination revealed a pale, vaginal mucosa. A small cystocele was present. The cervix was normal. On bimanual examination there was a sense of fullness in both fornices, more noticeable on the left. Rectal examination revealed no abnormalities. The findings in the extremities were essentially within normal limits. Neurologic examination was also within normal limits.

Preliminary fluoroscopy of the chest and x-ray films of the chest revealed a rounded, soft tissue density, measuring approximately 5 cm. in its greatest diameter, in the lateral aspect of the right mid-lung, which was adjacent and contiguous with the pleura, and which suggested loculated pleural fluid. There was a larger area of homogeneous density obscuring the entire left lower lung field, associated with pleural fluid in the left pleural space. In addition, there was a similar density in the superior medial aspect of the

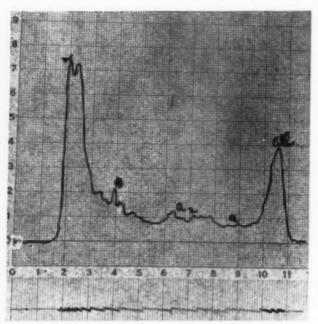


Fig. 1. Electrophoretic pattern of the blood serum shows a marked increase in the gamma globulin fraction.

right upper lung field, which also suggested encapsulated fluid. Spot roentgenograms for bony detail over the areas of density failed to demonstrate any definitive areas of bone destruction, demineralization, or other osseous abnormality in these zones. The initial impression was encapsulated fluid, associated with probable areas of pulmonary or pleuropulmonary metastases. A diagnostic thoracentesis was suggested.

Further radiographic studies of the abdomen, skull, sternum, scapula, pelvis and right femur revealed spotty areas of bone destruction, completely osteolytic and quite characteristic of the usual classical osseous changes seen in multiple myeloma. The sternum showed rather marked demineralization, with thinning of the cortices, without significant destruction, but there was a definite area of subpleural extension of myelomatous tumor arising from the posterior margin of the sternum. The liver and spleen were found to be slightly enlarged. Further detailed studies of the bony thorax again failed to demonstrate any evidence of bony involvement which could be construed to be myelomatous osseous change, with subpleural extension of tumor. The areas of pleuropulmonary involvement seemed to be completely limited to the pleura and the lung.

The urine had a specific gravity of 1.018, 3-plus albumin, was negative for sugar, and the sediment contained many fine granular casts per high power field, with 4 or 5 white cells and rare red cells per high power field. Three consecutive examinations for Bence Jones protein were negative. A Sulkowitch test for calcium was also negative. The hemoglobin on

admission was 7.5 gm. per cent with a cell volume of 26 per cent. The erythrocytes numbered 2,640,000 per cu. mm., white blood cells 6,250 per cu. mm. with 56 per cent small lymphocytes, 42 per cent mature neutrophils and 2 per cent eosinophils. The blood smears showed an increase in lymphocytes of the mature type, with excessive rouleaux formation. A Coombs' test was negative. The erythrocyte sedimentation rate (corrected) was 28 mm. per hour. The serum total cholesterol was 132 mg. per cent, alkaline phosphatase 1.7 units, phosphorus 3.7 mg. per cent. The prothrombin time was fifteen seconds, with a control of twelve seconds. A bromsulphalein test showed 7.5 per cent dye retention after forty-five minutes. Blood urea nitrogen was 23.9 mg. per cent. The serum total proteins were 8.4 gm. per cent of which serum globulin was 4.6 gm., serum albumin was 3.8 gm. The serum calcium was 9.0 mg. per cent. An electrophoretic pattern of the serum (Fig. 1) revealed a marked increase in the gamma globulin fraction, with a decrease in the albumin. The blood was negative for cryoglobulin. A bone marrow aspiration was performed and the smear consisted almost entirely of mature and immature plasma cells, some with as many as four nuclei. (Fig. 2.) The findings were quite compatible with the diagnosis of multiple myeloma.

Because of the massive pleural effusion in the left pleural cavity, thoracentesis was performed. (Fig. 3.) About 600 cc. of reddish tinged, slightly turbid fluid was obtained. The specific gravity was 1.030. A cell count revealed 95 per cent of the cells to be plasma cells, 1 per cent were polymorphonuclear leukocytes, 3 per cent large mononuclear cells and 1 per cent were small mononuclear cells. There were 30,000 erythrocytes per cu. mm. A sugar determination was 27 mg. per cent. No epithelial tumor cells were found. At a later date thoracentesis was performed in the right pleural cavity and the same type of pleural fluid was obtained. On microscopic examination many plasma cells were noted.

The patient was hospitalized for twelve days. During her stay her symptoms of weakness, anorexia, slight dyspnea and pain in the left lower anterior chest persisted. During the evening she complained of pain in the right hip, with radiation to the right knee. Night sweats were often present, but the temperature was within the limits of normal except for one day when a thoracentesis had been performed.

Treatment with urethane [2,6] was attempted but was abandoned after a total of 6 gm. had been given over a two-day period. Prior to therapy the leukocyte count was 6,238 per cu. mm., of which 56 per cent were small lymphocytes, but after the drug was given the leukocyte count decreased to 4,150 per cu. mm. with 72 per cent small lymphocytes, 3 per cent large lymphocytes and only 18 per cent mature neutrophils. She received 1,000 cc. of whole blood during her hospital stay, and the hemoglobin, on discharge, was

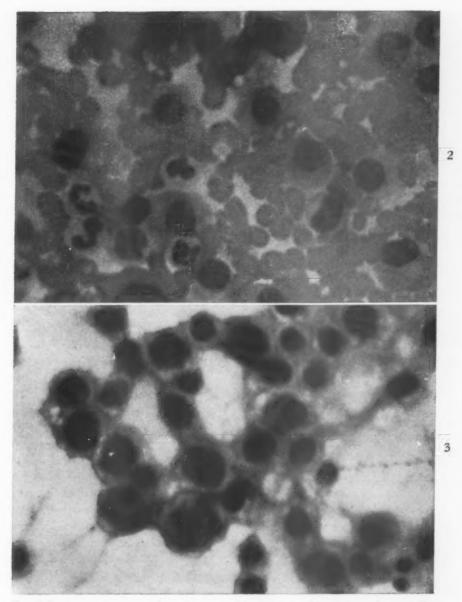


Fig. 2. Bone marrow smear shows innumerable mature and immature plasma cells. Fig. 3. The pleural fluid contained cells, 95 per cent of which were plasma cells.

9 gm. per cent with a cell volume of 28 per cent. The erythrocyte count was 2,750,000 per cu. mm.

X-ray therapy to the areas in the right mid-lung and left lower lung was administered, with approximately 2,500 r tumor dose to the area in the right mid-lung and 2,200 r tumor dose to the area at the left base, delivered in a twenty-eight-day period. The x-ray therapy was given with a conventional 250 KV therapy unit, with a beam of a half value layer of 3.25 mm. of copper. Rather striking regression of the areas of pulmonary infiltration and pleural pulmonary involvement occurred. (Figs. 4 and 5.)

In spite of the regression of the pulmonary involvement following x-ray therapy the patient continued to complain of considerable discomfort in the left lower side of the chest, with anorexia, weakness and weight loss. Blood studies showed the hemoglobin to vary from 6.9 gm. to 7.75 gm. per cent. The leukocyte count ranged from 5,000 to 6,800 per cu. mm. with a normal differential distribution. She also had generalized purpuric eruptions, with considerable pruritus. Platelet counts were 50,000 per cu. mm. on two occasions. It was then decided to try again to give her urethane, 1.0 gm. four times daily. She was also given triamcinolone, 4 mg. four times daily. Under this regimen of therapy there was a definite improvement in the chest pain. Appetite improved and she had a sense of well-being. The latest blood count, which was in July 1958, revealed a hemoglobin of 11 to 12 gm. per cent, an erythrocyte count of 4,000,000 per cu.

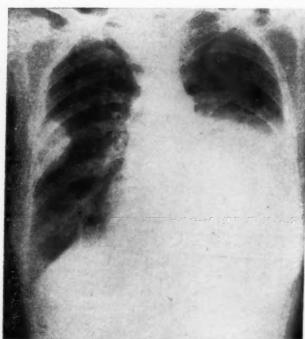
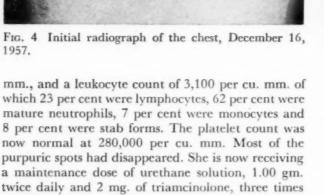


Fig. 4 Initial radiograph of the chest, December 16, 1957.



COMMENTS

daily. She had been receiving these medications for

two months.

Multiple myeloma was first suspected when excessive rouleaux formation was reported in a peripheral blood smear. Further confirmatory evidence was given by the typical electrophoretic pattern of the serum proteins. The classical roentgenographic findings of multiple myeloma were found in the left scapula, right femur, ischium and skull. The presence of numerous plasma cells in the pleural fluid and bone marrow was diagnostic.

As already indicated, pulmonary involvement in multiple myeloma is uncommon. Extraosseous pleural involvement is even more rare. In a report of fifty-one cases Meacham [3] found no cases of isolated pleural involvement, and a limited search of the literature failed to uncover any other instances. Pleural involvement is reported by Snapper [2] and Batts [5] and occurs when plasmacytomas of ribs or sternum

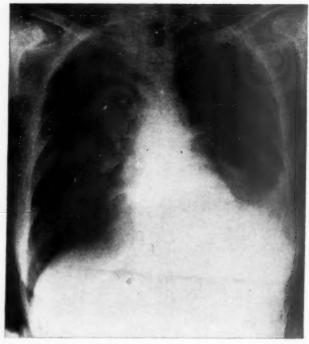


Fig. 5. Radiograph of the chest after x-ray therapy February 20, 1958.

infiltrate the subpleural space by direct extension. Detailed x-ray examination in this instance failed to demonstrate any significant bony change in the areas of contiguous pleural involvement. Paramyloid masses would seem to be unlikely in this instance, as there were no clinical manifestations of amyloidosis of the skin, joints, heart or gastrointestinal tract. The involvement in the right lung is probably a pleural plasmacytoma and the area in the left lung a subpleural and pulmonary parenchymatous plasmacytoma.

Frequent colds with fever and coughing, as reported by this patient, occur in those suffering from multiple myeloma [1]. The absence of the common antibodies in the abnormal globulin fraction of the myeloma serum leaves these patients unprotected against infections. The sluggishness of the blood flow through the lungs due to the marked increase in blood viscosity and rouleaux formation of the red cells must facilitate the development of pneumonia. Recurring pneumonitis in adults should suggest the possibility of hypogammaglobulinemia, such as occurs in myeloma.

SUMMARY

A case of multiple myeloma is reported which presented dominant pleuropulmonary manifestations. The pulmonary pathology was

probably due to pleural plasmocytomas, with subpleural and pulmonary parenchymal myelomatous involvement.

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Postural Hypotension*

Report of a Case, with Hemodynamic Studies of Central, Peripheral and Pulmonary Artery Pressures

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Profound alterations of the normal hemodynamic responses have been described in patients with postural hypotension, including abnormal changes referable to arteriolar resistance, venous tone, cardiac output and neurohormonal vasopressor substances. These changes generally have been related to the circulatory abnormalities occurring in the erect position. The purpose of this report is to present a patient with postural hypotension who had previously undescribed abnormal circulatory findings which were present in the recumbent as well as in the upright position, and to record the circulatory responses of this patient to posterior pituitary preparations and to desoxycorticosterone acetate (DOCA®).

CASE REPORT

J. Mc., a forty-two year old housewife, was admitted to The Mount Sinai Hospital on January 20, 1958, complaining of weakness and dizziness upon standing.

In 1954, the patient was diagnosed as having diabetes mellitus and control of the diabetes was achieved with the administration of 20 units of NPH insulin daily. In October 1957, the patient first experienced weakness and dizziness upon standing. Her symptoms were immediately relieved by returning to the recumbent position.

Concomitantly, severe vomiting developed and she was admitted to another hospital in diabetic acidosis. Treatment with intravenous fluids and additional insulin readily corrected the acidosis, but because of persistent vomiting an exploratory laparotomy was performed. A congenitally absent right adrenal gland and kidney were noted but no intra-abdominal disease was found. Postoperatively, the vomiting subsided; however, her incapacitating postural symptoms persisted, necessitating further hospitalization.

On admission to The Mount Sinai Hospital, the patient was thin and appeared chronically ill. The physical examination was within normal limits with the exception of her response to the upright position. The patient's blood pressure in the recumbent position was 110/70 mm. Hg; in the sitting position it was 80/50 mm. Hg. On assuming the erect position, she became weak and dizzy, but did not lose consciousness; her blood pressure was unobtainable, but her pulse rate remained unchanged.

Neurological examination revealed the deep tendon reflexes in the lower extremities to be absent, but sensation was intact. The peripheral sweating response was diminished.

Routine studies of the blood and stool revealed no abnormalities. There was moderate acetonuria without glycosuria and a hypochloremic alkalosis, attributed to her recent vomiting. The cerebrospinal fluid protein content was increased to 67 mg. per 100 cc., but the spinal fluid was otherwise normal. Urinary catecholamines, calculated as norepinephrine, were 18 µg. per twenty-four hours, the lower limit of normal. Results of studies of adrenal cortical function, including a water-loading test, urinary 17-ketosteroids and blood 17-hydroxycorticoids, were normal. Roentgenograms of the chest and gastro-intestinal system showed no abnormalities.

Studies of the central and peripheral pressure and of pulmonary artery pressure were carried out on a tilttable in order to investigate the patient's severe, disabling postural hypotension. A No. 7 cardiac catheter was passed under fluoroscopic control from the right antecubital fossa to the right pulmonary artery. To record central arterial pressures, a polyethylene catheter was advanced to the ascending aorta just above the aortic valve through a thin-walled 18G needle inserted percutaneously into the left femoral artery. Peripheral arterial pressures were recorded via a Cournand needle inserted percutaneously into the left brachial artery. The zero point for all pressures was 5 cm. posterior to the sternal angle, irrespective of the position of the tilt-table. The systemic pressures were recorded simultaneously from a single base line by means of Statham strain gauges set at equal sensitivities.

The catheterization studies are recorded in Figure 1. In the upper portion of the figure, the pronounced fall in both central and peripheral pressures is evident, the

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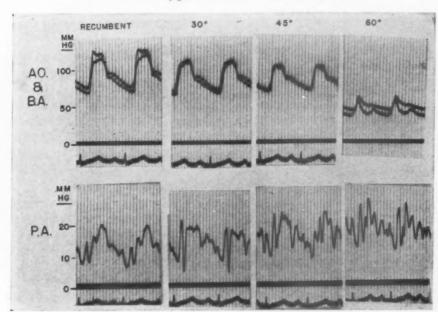


Fig. 1. Simultaneously obtained central aortic and brachial arterial pressure. The pulmonary arterial pressures were recorded immediately following recording of the systemic pressures. The systemic pressures were recorded from a single base line, the strain gauges being set at equal sensitivities. The central pressure is identified by its earlier onset. In the upper portion of the figure, the pronounced fall in arterial pressure with tilting is evident. In contrast to a normal patient, the central systolic pressure was slightly higher than the peripheral systolic pressure during recumbency. During tilting at 60 degrees, although the peripheral pressure was slightly higher than the central pressure, the difference between the two pressures was smaller than seen in normal patients. In the lower portion of the figure the changes occurring in the pulmonary arterial pressure are demonstrated. In contrast to the systemic circulation, the pressure in the pulmonary artery rises slightly during tilting.

most marked drop coming at a 60 degree tilt. These findings are of course definitely abnormal, the normal response to tilting being a slight fall in systolic pressure, a rise in diastolic pressure and a fairly constant mean pressure. The relationship of the central aortic to the peripheral arterial pressure in this patient is of interest. Whereas normally in the recumbent position the brachial artery systolic pressure exceeds the central aortic systolic pressure by about 10 per cent and the peripheral pulse pressure exceeds the central pressure by about 40 per cent [1], in this patient the central systolic pressure was slightly higher than the peripheral systolic pressure. During tilting of the normal patient the difference between the two pressures is markedly accentuated [1]. In this patient, although the peripheral pressure was slightly higher than the central pressure at 60 degrees, the difference between the two pressures was smaller than would be evident in a normal subject. The lower portion of Figure 1 shows the changes occurring in the pulmonary arterial pressure recorded immediately after recording of systemic pressure. In contrast to the systemic circulation, the pressure in the pulmonary artery rose slightly during tilting.

The patient was given posterior pituitary prepara-

tions to evaluate the effect on her postural hypotension. A Pitressin® infusion, 3 mu. (milliunits) per minute, produced a maximum pressor response in both the recumbent and erect positions. (Table 1.) However, 5 units of Pitressin tannate in oil administered subcutaneously did not maintain her blood pressure while standing. The intravenous administration of 10 units of oxytocin had no effect on the blood pressure.

Attempts to treat the patient's postural hypotension with the use of elastic stockings, an abdominal binder, ephedrine 30 mg. four times daily, and atropine to tolerance were unavailing. The intramuscular administration of mephentermine (15 mg.) produced a pressor response in the recumbent position, but had no effect on the postural hypotension. (Table I.)

DOCA (5 mg.) was administered intramuscularly twice daily. Within seventy-two hours a slight hypertensive effect was achieved in the recumbent position, and the patient's blood pressure was maintained fairly close to normal levels in the erect position. For the first time in several months she was able to walk without difficulty. When the patient did not receive the drug for several days the postural hypotension returned. When DOCA therapy was reinstituted, the

Table 1

BLOOD PRESSURE RESPONSE TO VARIOUS PHARMACOLOGICAL
AGENTS IN THE RECUMBENT, SITTING AND STANDING
POSITIONS

	POSITIONS			
Data	Blood Pressure (mm. Hg)			
	Recumbent	Sitting	Standin	
	Untreated			
	110/70	80/60	0/0	
Pitressi	n (Intravenous	Infusion)		
1 mII /min	160/110	130/100	90/60	
1 mU./min			110/80	
2 mU./min			140/90	
3 mU./min	******			
4 mU./min	******		125/90	
Pitressin Tannate	e in Oil (5 Un	its Subcutane	ously)	
10 min	120/70		0/0	
15 min	100/70		0/0	
30 min	90/60		0/0	
60 min	90/70		0/0	
Oxytocin	(10 Units Intr	avenously)		
30 sec	60/40			
1 min	70/50			
2 min	85/70	******		
5 min	95/70			
Mephentermi	ne (15 mg. Inti	ramuscularly)		
45 min	150/90	120 /90	70 /0	
45 min	150/80 150/80	120/80	70/0	
bu min	150/80	130/90	40/0	
DOCA (5 mg. Intramu.	scularly)		
Day 1	120/70	100/70	80/60	
Leady Recessors				
Day 2	130/80	110/70	80/60	

beneficial therapeutic effect was again achieved without weight gain or other undesirable side effects of the drug.

The patient was discharged from the hospital and took 15 units of NPH insulin daily and 2 and ½ mg. of sublingual DOCA twice daily. For a two-month period she continued to walk and function normally, but subsequently orthostatic hypotension developed again despite maintenance doses of DOCA. After an interval of several weeks she again responded satisfactorily to the administration of 5 mg. DOCA daily.

COMMENTS

Postural hypotension has been found as an isolated occurrence and in association with various endocrinological and neurological disease states. The association of postural hypotension with diabetes mellitus is well known and has been considered to be a form of autonomic neuropathy simulating a sympathectomy [2-4]. This diabetic patient exhibited postural hypotension and in addition an abnormal sweating response, absent deep tendon reflexes in the lower extremities, pernicious vomiting and an elevated cerebrospinal fluid protein content. All these findings have been described as manifestations of diabetic neuropathy, and are more commonly found in patients with long-standing diabetes and diabetic complications of other organ systems [4]. Fagerberg [5] believes that the neuropathy is secondary to a specific vascular lesion, whereas Rundles [4] attributes its occurrence to the abnormal metabolic state of chronically unregulated diabetes. The precise cause of the syndrome in diabetic subjects, however, is not well known as morphological studies in these patients are scanty.

Catheterization studies afforded the opportunity to identify further the abnormal circulatory phenomena occurring in these patients. The results in this patient differed considerably from those observed in the normal subject as reported by Kroeker and Wood [1]. As opposed to the normal response, in this patient central arterial systolic pressure exceeded peripheral arterial pressure in the recumbent position. After tilting to 60 degrees, both central and peripheral arterial pressures fell considerably, and the peripheral systolic, diastolic and mean pressures exceeded the corresponding central pressures. However, abnormalities in the relationship between the two pressures are evident at a 60 degrees tilt as well as during recumbency since the difference between the two pressures is considerably less than would be evident in a normal person, and the brachial and aortic pulse pressures remained equal. Since the normal differences in amplitude and contour between the central and peripheral arterial pulses are believed to be due to summation of the initial wave with the reflected wave from the periphery, and since the normal relationship between the two pressures during tilting is generally attributed to compensatory vasoconstriction, it probably can be assumed that in this

patient peripheral vascular "tone" was considerably impaired in recumbency as well as during tilting. This implies a more faulty vasomotor state in this particular form of postural hypotension than has previously been stressed. In this regard, it is of interest that an increase in blood pressure with Pitressin infusion was obtained by Wagner and Braunwald [6] in patients with postural hypotension in the recumbent position whereas this drug had no effect in normal patients.

Several investigators have demonstrated abnormal vascular responses in patients with postural hypotension. Stead and Ebert [7] and Ellis and Haynes [8] postulated that the fundamental physiological defect in these patients is failure to respond to the normal amount of venous pooling in the upright position with an appropriate degree of reflex arteriolar constriction. MacClean and Allen [9], on the other hand, concluded that the defect in postural adaptation is not due to failure of arteriolar constriction but is related to inadequate venous return and diminished cardiac output. Hickam and Pryor [10] attempted to evaluate the relative importance of changes in cardiac output and of peripheral resistance in producing orthostatic fall in blood pressure. Although the results in their twelve patients were quite variable, significant postural hypotension was more consistently associated with failure of arteriolar constriction than with an abnormal decline in cardiac output. Nevertheless, they were able to prevent the drop in blood pressure in the erect position by serum albumin infusions. Loss of reflex venoconstriction in postural hypotension was postulated in these and in subsequent studies by Page and his associates [11].

In regard to the pathogenesis of the postural hypotension in this patient, the changes recorded in the pulmonary artery pressure, as demonstrated in Figure 1, are of considerable interest. In contrast to the events occurring in the systemic circulation, the simultaneously obtained pressure in the pulmonary artery rose slightly during tilting. Although the significance of this finding is difficult to interpret without more data, it does suggest that there probably was not, at least initially, a large drop in venous return, because under such circumstances one would not expect the pulmonary arterial pressure to rise unless there were a marked concomitant increase in pulmonary vascular resistance. The possibility of selective "compensatory" pulmonary vasoconstriction acting to sustain the pulmonary arterial pressure in the presence of impaired peripheral vasoconstriction is interesting to consider, but data to confirm this hypothesis have not yet been obtained.

Inasmuch as the physiologic mechanisms responsible for the symptoms of postural hypotension have not been precisely delineated, there have been varied approaches to therapy. Abdominal and leg binders have been suggested to prevent venous pooling but they were without effect in this patient, as were vasopressor agents. As emphasized in the report of Wagner and Braunwald [6], intravenously administered Pitressin was effective in relieving the postural hypotension of this patient, but it was not possible to work out a satisfactory and effective regimen of intramuscular injections. This might be a matter of precise adjustment of dosage, however.

The use of DOCA in the treatment of orthostatic hypotension, which was effective in this patient, was previously reported by Spingarn and Hitzig [12] and by Gregory [13]. The reason for the efficacy of DOCA in this syndrome is somewhat obscure, although it has been attributed to an increase in blood volume and also of extravascular volume which might act to prevent pooling of blood in dependent areas. Raab and his associates [14], however, found no significant increase in the body weight of normal subjects with DOCA-induced hypertension. They have also shown that the pressor effect of infused epinephrine and norepinephrine is potentiated in man by pretreatment with DOCA. This effect was further exaggerated by increasing the sodium intake, and diminished or abolished by rigid sodium restriction. The varying response of this patient to the same dose of DOCA may have been due to alterations in her salt intake, but this factor was not controlled accurately enough to provide precise information on this point.

SUMMARY

A patient with diabetic neuropathy and associated orthostatic hypotension is described.

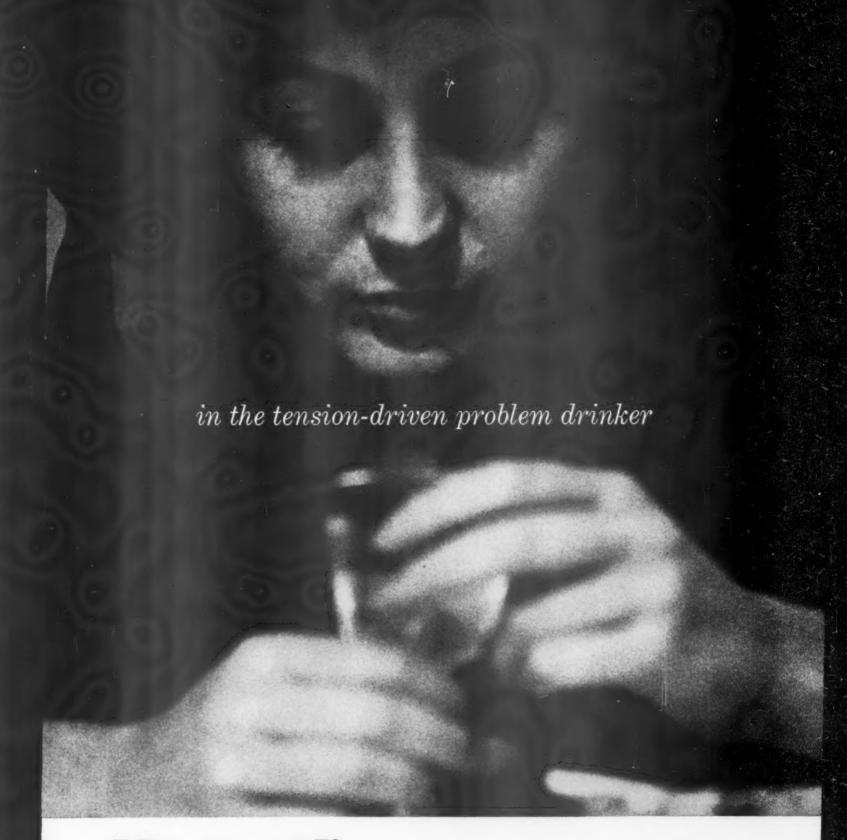
Cardiac catheterization studies of central and peripheral arterial pressures during various degrees of tilting revealed abnormal findings in the recumbent position as well as during tilting. Whereas normally the peripheral arterial pressure exceeds the central arterial pressure, in this patient the central arterial pressure was slightly higher than the peripheral arterial pressure in the recumbent position. During tilting, the peripheral arterial pressure exceeded the central arterial pressure but the difference between the pressures was considerably less than would be evident in a normal person. These findings were taken as evidence that peripheral vascular "tone" was impaired in this patient in recumbency as well as during tilting. A simultaneously recorded pulmonary arterial pressure demonstrated a slight rise during tilting in contrast to the events in the systemic circulation, suggesting that there was no large initial fall in venous return.

Pressor effects and relief of postural hypotension were obtained with Pitressin, administered intravenously, as well as with DOCA, administered intramuscularly. Sublingual administration of DOCA resulted in a prolonged remission.

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REFERENCES: 1. Ayd, F. J., Jr.: Current Therapeutic Research 1:41 (Oct.) 1959.

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For a preview of the change Aldactone is expected to make in the treatment of edema, please turn the page.

What Physicians May Expect of

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Furthermore, when Aldactone is used in conjunction with a mercurial or thiazide diuretic the level of satisfactory response may be expected to rise to approximately 85 per cent in those whose condition was refractory to all previously available therapeutic measures.

The response of some patients with extremely resistant edema may be further enhanced by administering a glucocorticoid such as prednisone. When Aldactone is used in such a comprehensive therapeutic regimen a satisfactory diuresis and relief of edema may be expected in more than 90 per cent of edematous patients who would not otherwise respond.

DOSAGE: For most adult patients the optimal dosage of Aldactone, brand of spironolactone, is 400 mg. daily in divided doses. Aldactone should be administered for at least four or five days before appraising the response, since the onset of its therapeutic effect is gradual when the drug is used alone. When used in combination with mercurial or thiazide diuretics Aldactone manifests greater activity on the first and second days. The dosage range is 300 to 1,200 mg. daily and dosage should be adjusted to the response of the patient. A dosage of 400 mg. daily, however, will meet the requirements of most patients, and even 800 mg. daily will seldom be required.

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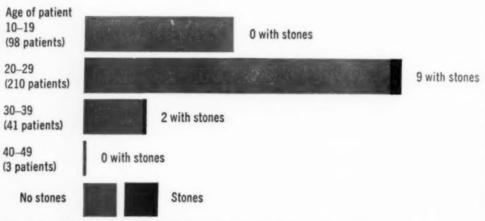


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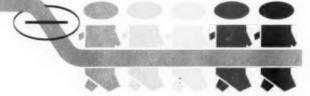
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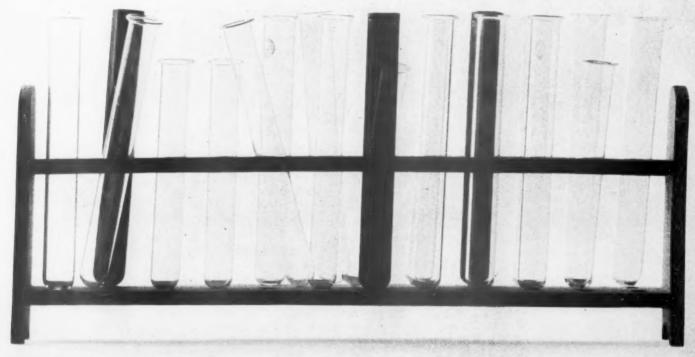
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1. Romansky, M. J., Ristocetin, Antibiotics Monographs, No. 12, New York, Medical Encyclopedia Inc., 1959.







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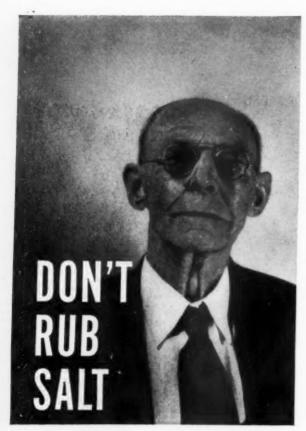
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in the enteric-coated core:

Pancreatin,	N.	F		 0		٠	 						.300	mg.
Bile salts			0 0		 		 		0	0	9		.150	mg.

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In each yellow enteric-coated PABALATE tablet:

Sodium sa	alicylate (5 gr.)	0.3	Gm.
Sodium pa	ra-aminobenzoate (5 gr.)	0.3	Gm.
Ascorbic a	cid	50.0	mg.

For the patient who should avoid sodium

PABALATE-SODIUM FREE

Same formula as Pabalate, with sodium salts replaced by potassium salts (pink)

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Pabalate with Hydrocortisone

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Potassium salicylate (5 gr.)	0.3 Gm.	
Potassium para-aminobenzoate (5 gr.)	0.3 Gm.	
Ascorbic acid	50.0 mg.	

1. Ford, R. A., and Blanchard, K.: Journal-Lancet 78:185, 1958.

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References:
1. Yü, T. F., Burns, J. J., and Gutman, A. B.:
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17:326, 1958. 4. Ogryzlo, M. A., and Harrison,
J.: Ann. Rheumat. Dis. 16:425, 1957.

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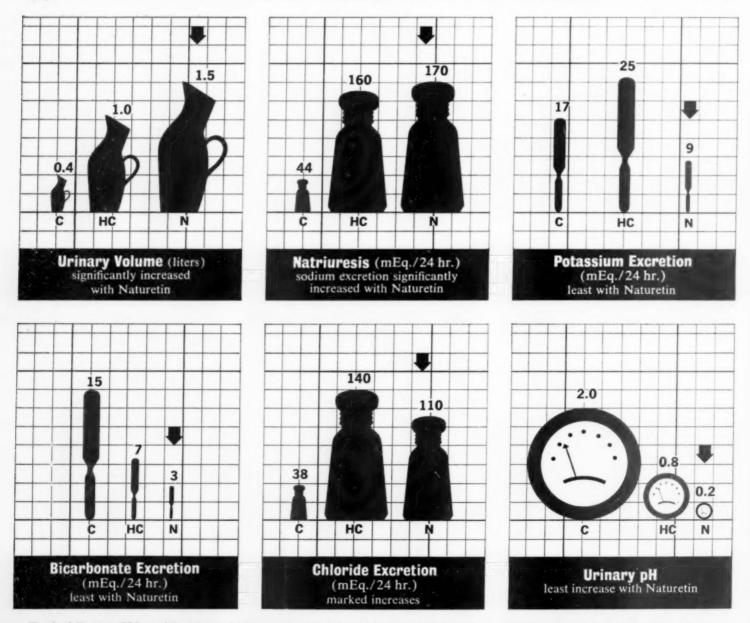
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"When compared to other members of this heterocyclic group of compounds, this drug [NATURETIN] shows a significantly increased natriuresis and decreased loss of potassium and bicarbonate. In this respect it more closely approaches a natural or 'ideal diuretic.' It is effective upon continuous administration and causes no significant serum biochemical changes. It is effective in a wide variety of edematous and hypertensive states and represents a significant advance in diuretic therapy." Ford, R.V.: Pharmacological observations on a more potent benzothiadiazine diuretic; accepted for publication by the American Heart Journal.

Comparison of electrolyte excretion pattern for the 24 hours following typical doses of chlorothiazide, hydrochlorothiazide, and Naturetin¹



Typical Doses: Chlorothiazide -1,000 mg.; Hydrochlorothiazide -50 mg.; Naturetin (Benzydroflumethiazide) -5 mg.

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- low daily dosage more economical for the patient
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- greater potency mg. for mg.—more than 100 times as potent as chlorothiazide
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- low toxicity few side effects low salt diets not necessary
- comparative studies with chlorothiazide, hydrochlorothiazide, and Naturetin disclose that smallest doses of Naturetin produce greater weight loss per day
- in hypertension, Naturetin, alone or in combination with other antihypertensives, produces significant decreases in mean blood pressure and other favorable clinical effects
- purpura and agranulocytosis not observed
- allergic reactions rarely observed

²Reports (1959) to the Squibb Institute for Medical Research.

Naturetin — Indications: in control of edema when diuresis is required, in congestive heart failure, in the premenstrual syndrome, nephrosis and nephritis, cirrhosis with ascites, edema induced by drugs (certain steroids); in the management of hypertension, used alone, combined with Raudixin (Squibb Rauwolfia Serpentina Whole Root), or with other antihypertensive drugs, such as ganglionic blocking agents.

Contraindications: none, except in complete renal shutdown.

Precautions: when Naturetin is added to an antihypertensive regimen including hydralazine, veratrum, and/or ganglionic blocking agents, immediate reduction must be made in the dosage for all preparations; the dosage for ganglionic blocking agents must be decreased by 50% to avoid a precipitous drop in blood pressure. This also applies if these hypotensive drugs are added to an established Naturetin regimen . . . in hypochloremic alkalosis with or without hypokalemia . . . in cirrhotic patients or those on digitalis therapy when reductions in serum potassium are noted . . . in diabetic patients or those predisposed to diabetes . . . when increased uric acid concentrations are noted . . . when signs—leg or abdominal cramps, pruritus, paresthesia, rash—suggestive of hypersensitivity, are noted.

Naturetin — Dosage: in edema, average dose, 5 mg., once daily, preferably in the morning; to initiate therapy, up to 20 mg., once daily or in divided doses; for maintenance, 2.5 to 5.0 mg., daily in a single dose. In hypertension: suggested initial dose, 5 to 20 mg. daily; for maintenance, 2.5 to 15 mg. daily, depending on the individual response of the patient. When Naturetin is added to an antihypertensive regimen with other agents, lower maintenance doses of each drug should be used.

Naturetin - Supplied: tablets of 2.5 mg. and 5 mg. (scored).

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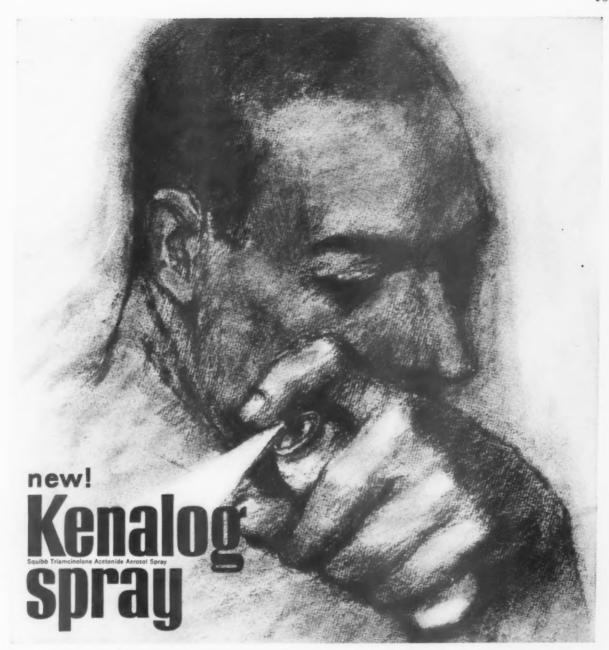
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Dosage: Apply the spray to the affected areas from a distance of 3 to 6 inches, t.i.d. or q.i.d. A 3-second spray (delivering approximately 0.1 mg, of triamcinolone acetonide) covers an area about the size of the hand. Cover the eyes when using Kenalog Spray on or near the face.

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References: 1. Reports to the Squibb Institute for Medical Research. 2. Howell, C. M.: Squibb Clin. Res. Notes 1:5 (Oct.) 1938. 3. Goodman, J. J.: Squibb Clin. Res. Notes 1:1 (Oct.) 1938. 4. Smith, J. G., Jr.: Zawisza, R. J., and Blank, R.: Squibb Clin. Res. Notes 1:1 (Oct.) 1938. 5. Fitspatrick, T. B.; Crowe, F. W., and Walker, S. A.: Squibb Clin. Res. Notes 1:2 (Oct.) 1938. 6. Lerner, A. B.: Squibb Clin. Res. Notes 1:2 (Oct.) 1958. 7. Rebinson, R. C. V.: Bull. School of Med, U. Maryland 43:54 (July) 1958.



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C. W., et al.: South, M. J.

and Bryans, C. I., Jr.:

10. Report of study by Army, Navy, Air Force Motion Sickness Team: J.A.M.A. 160:755, 1956.



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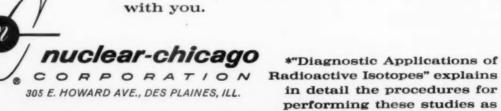
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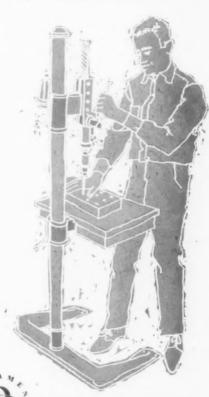
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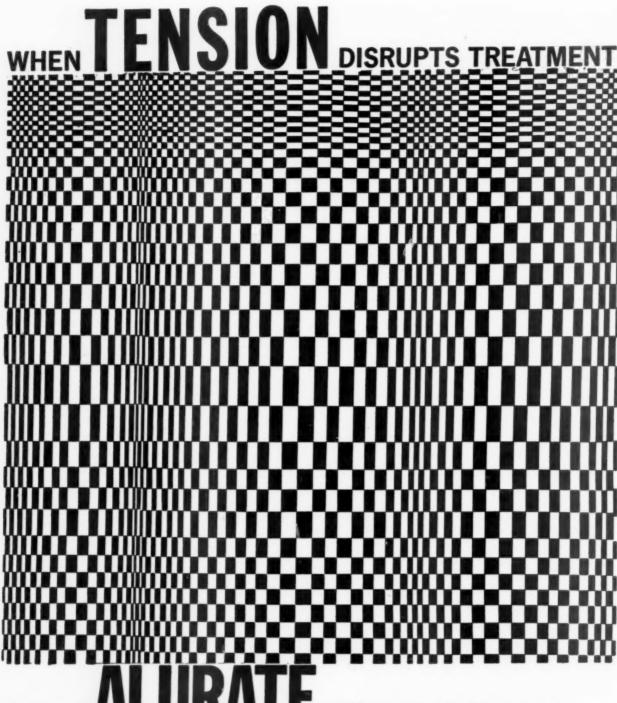
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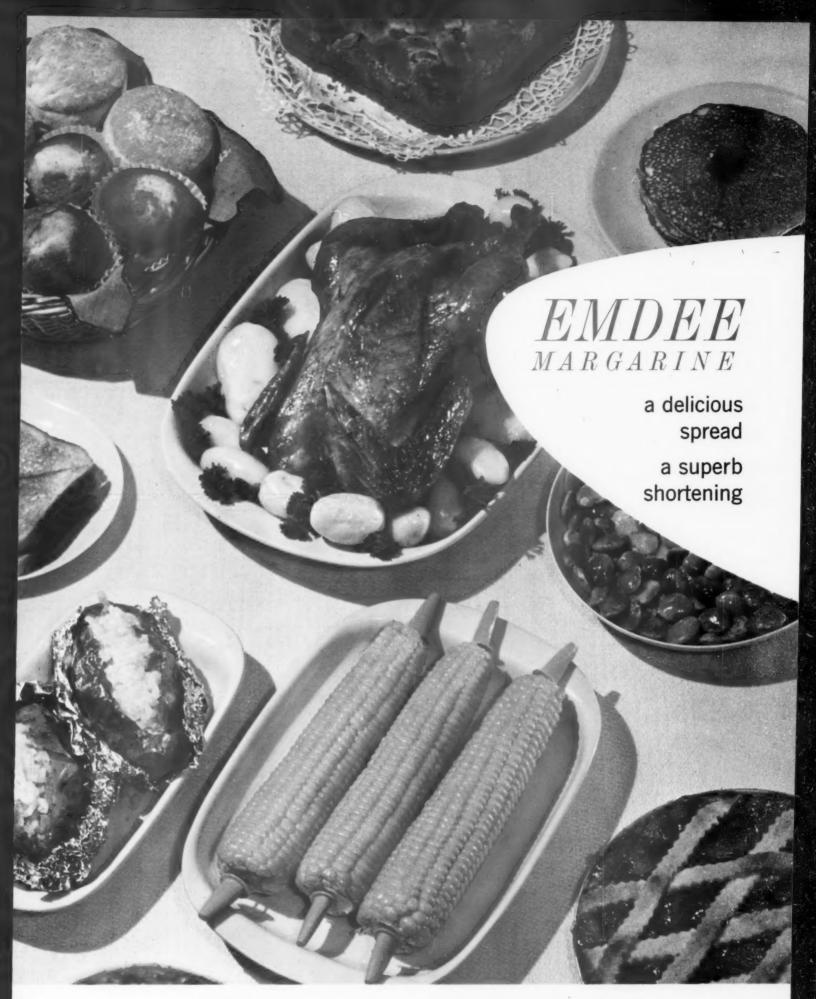
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References: 1. Terman, L. A.: Dietary management of hypercholesterolemia, Geriatrics 14:111 (Feb.) 1959. 2. Boyer, P. A.; Lowe, J. T.; Gardier, R. W., and Ralston, J. D.: A new dietary management of hypercholesterolemia, J.A.M.A., in press. 3. Vail, Gladys E.: Cooking with fats high in polyunsaturated fatty acids, J. Am. Dietet. A. 35:119 (Feb.) 1959.

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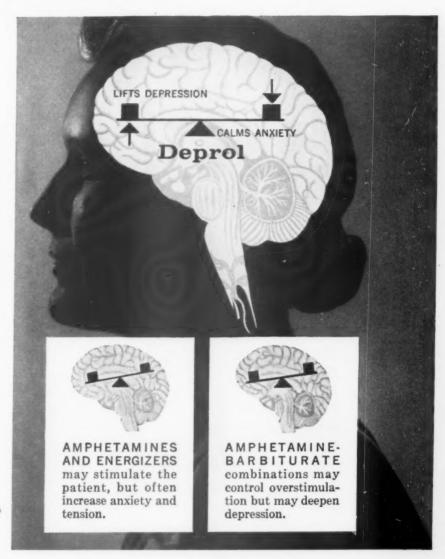
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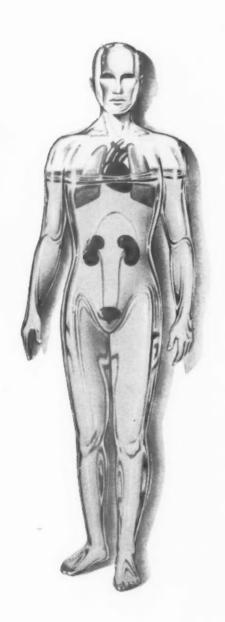
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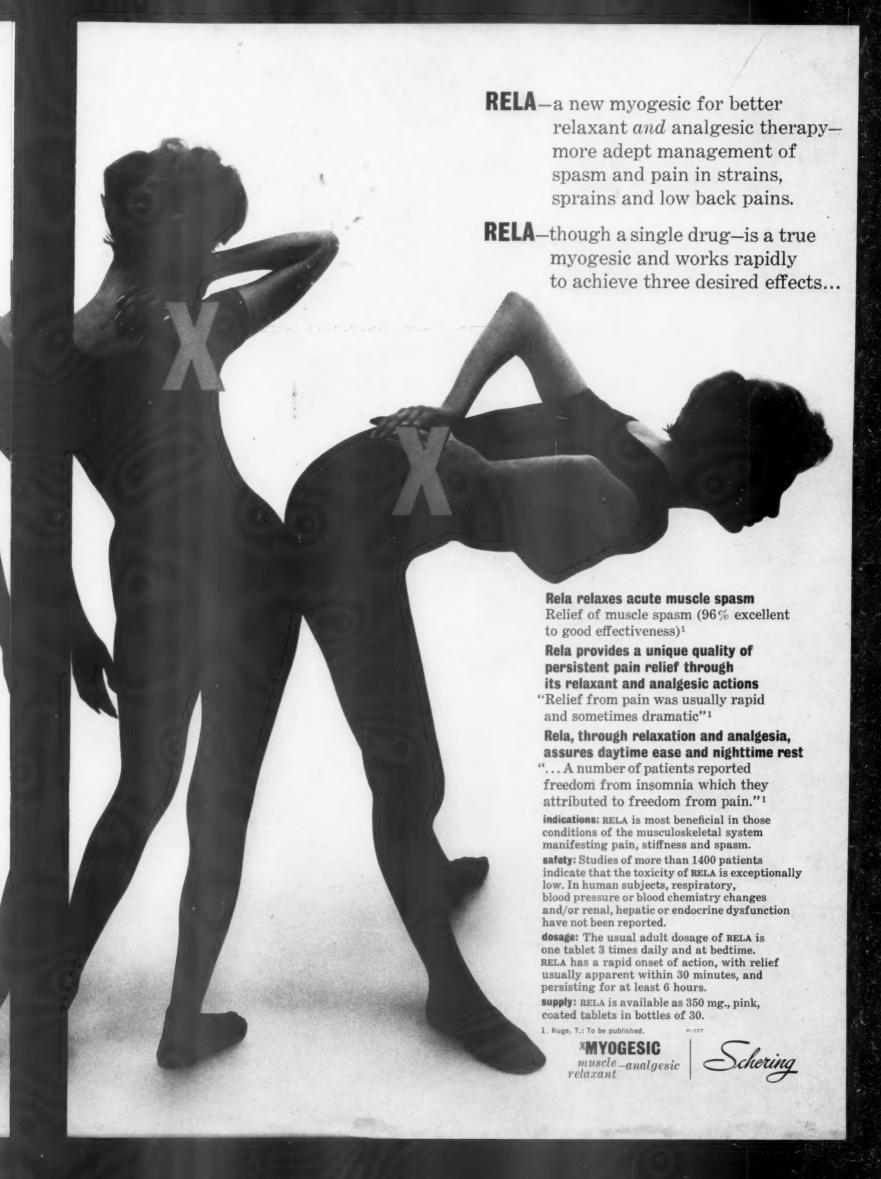
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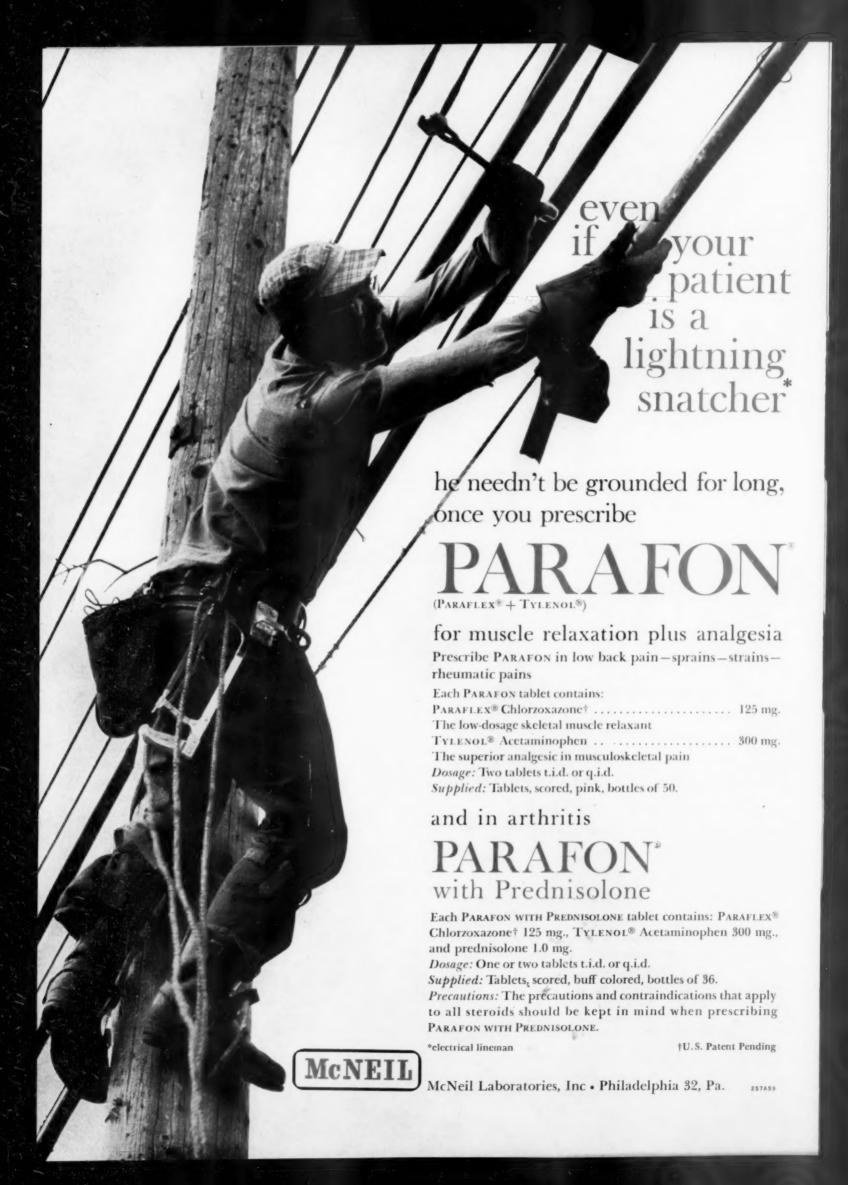


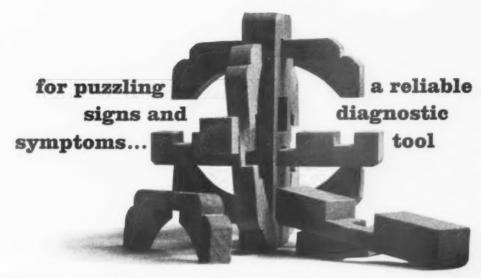
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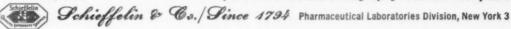
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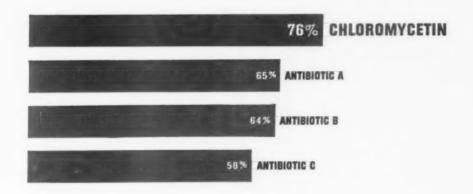
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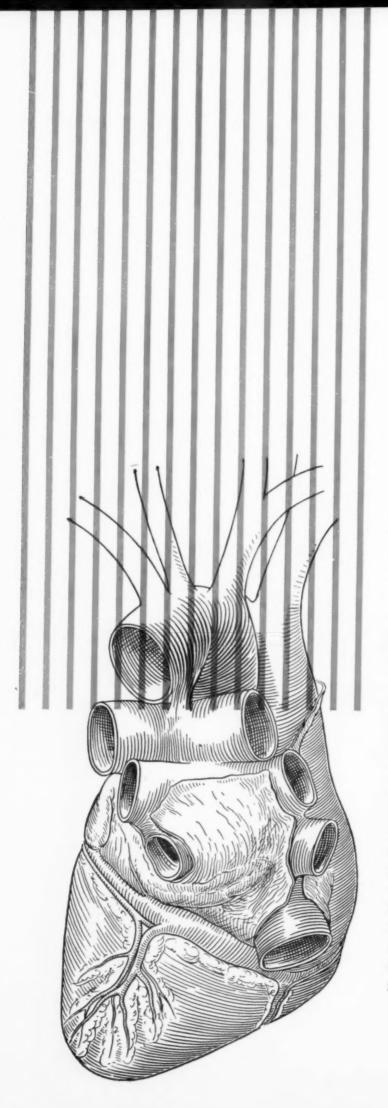
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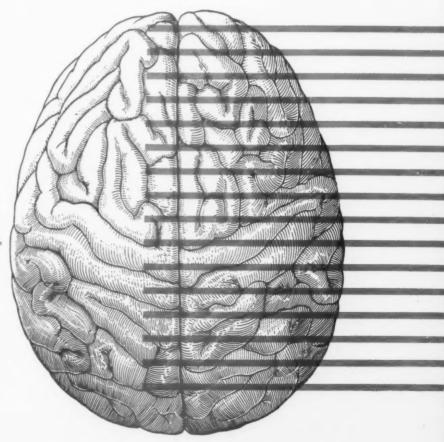
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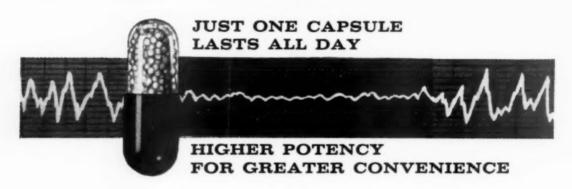


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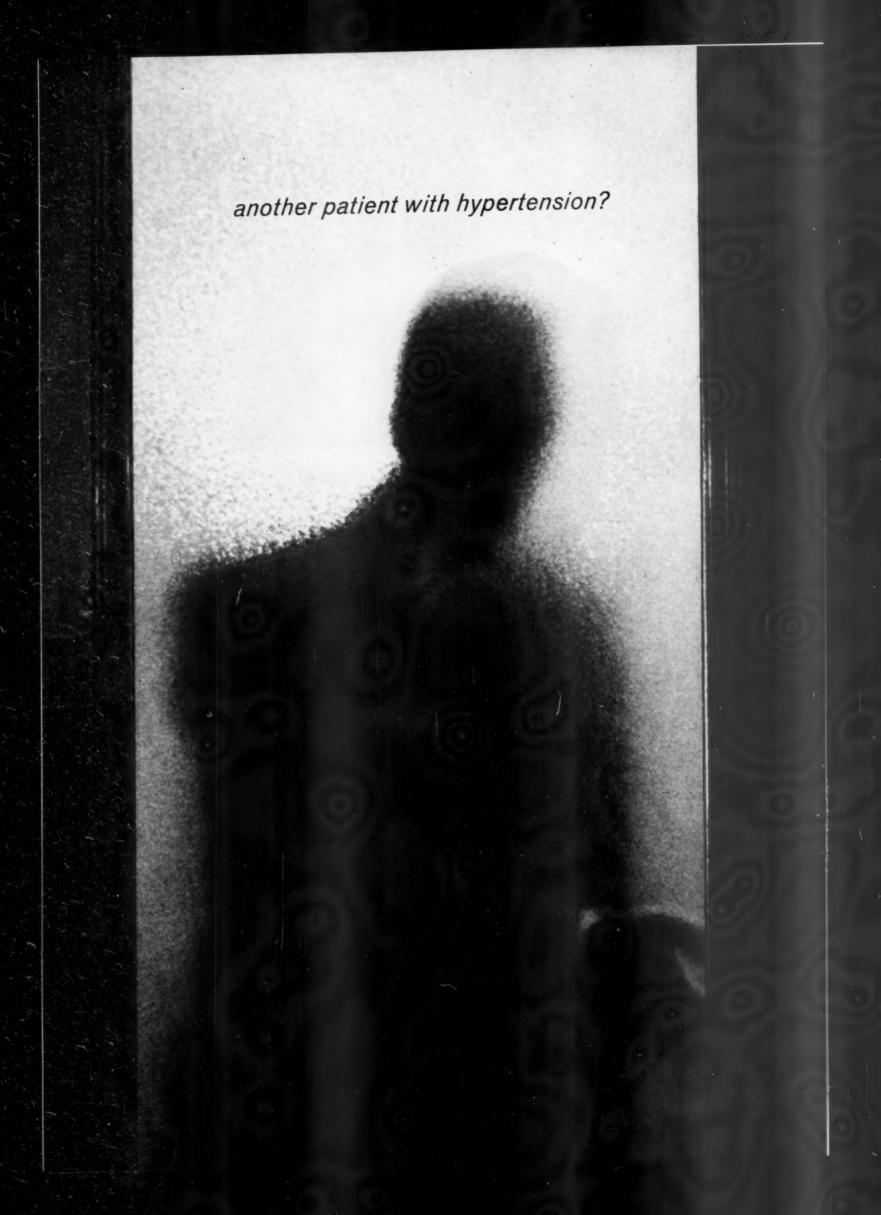
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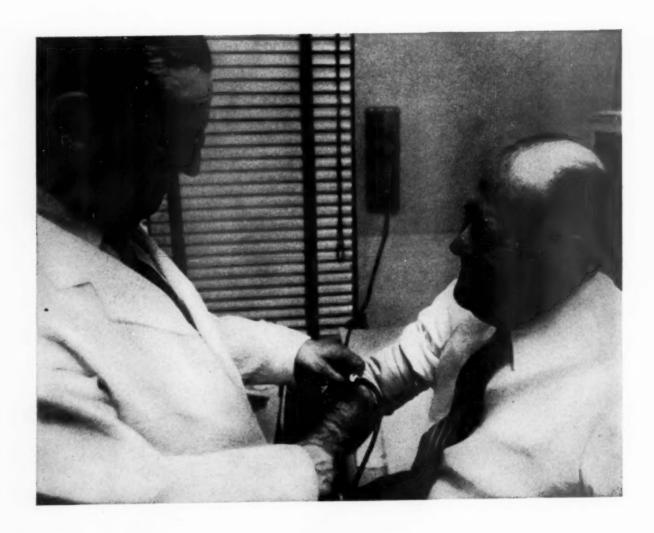
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Lysaught, J. N., and Cleaver, W.: Paper presented at the Symposium on Antibacterial Therapy, Michigan and Wayne County Academies of General Practice, Detroit, Sept. 12, 1959 (published Nov., 1959)

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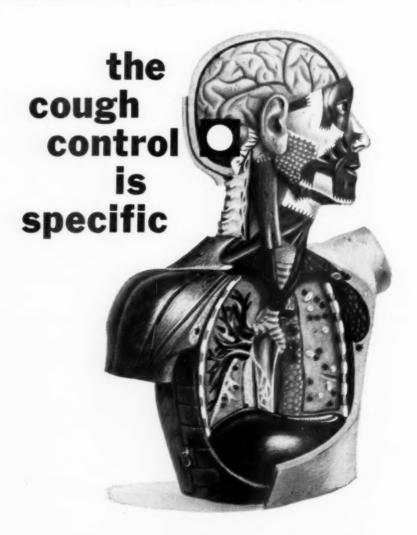
REFERENCES: 1. H. A. Bickerman in W. Modell, Ed., Drugs of Choice 1958-1959, St. Louis, The C. V. Mosby Company, p. 557. 2. L. J. Cass and W. S. Frederik, New England J. Med., 249:132, 1953. 3. L. J. Cass, W. S. Frederik and J. B. Andosca, Am. J. M. Sc., 227:291, 1954. 4. H. Isbell and H. F. Fraser, J. Pharmacol. & Exper. Therap., 107:524, 1953. 5. W. M. Benson, P. L. Stefko and L. O. Randall, J. Pharmacol. & Exper. Therap., 109:189, 1953. 6. New and Nonofficial Drugs 1959, Philadelphia, J. B. Lippincott Company, 1959, p. 326. 7. N. Ralph, Am. J. M. Sc., 227:297, 1954. 8. H. A. Bickerman, E. German, B. M. Cohen and S. E. Itkin, Am. J. M. Sc., 234:191, 1957.

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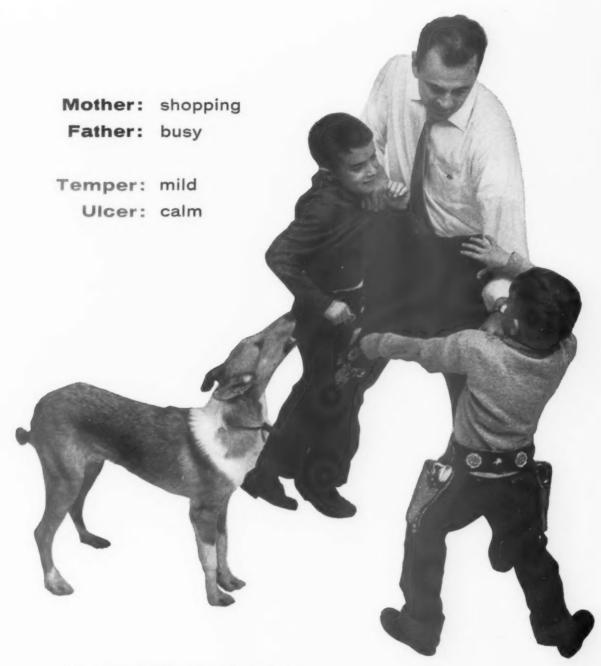
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References: 1. Cronk, G. A.; Naumann, D. E., and Casson, K.: Antibiotics Annual 1957-1958, New York, Medical Encyclopedia, Inc., 1958, p. 397. 2. Childs, A. J.: Brit. M. J. 1:660 (Mar. 24) 1956. 3. Newcomer, V. D.; Wright, E. T., and Sternberg, T. R.: Antibiotics Annual 1954-1955, New York, Medical Encyclopedia, Inc., 1955, p. 686.

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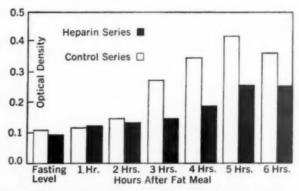
Dosage: After each meal, hold one tablet under the tongue until dissolved.

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- 1. Fuller, H. L.: Angiology 9:311 (Oct.) 1958.
- 2. Shaftel, H. E., and Selman, D.: Angiology 10:131 (June)



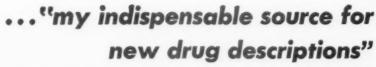
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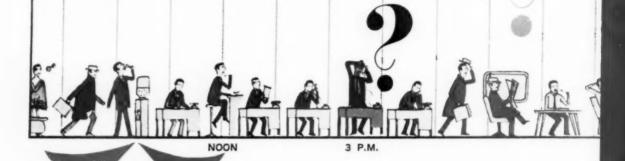
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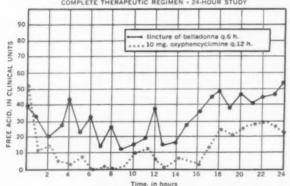
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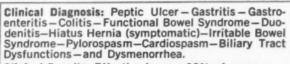




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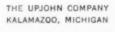
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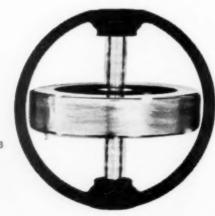


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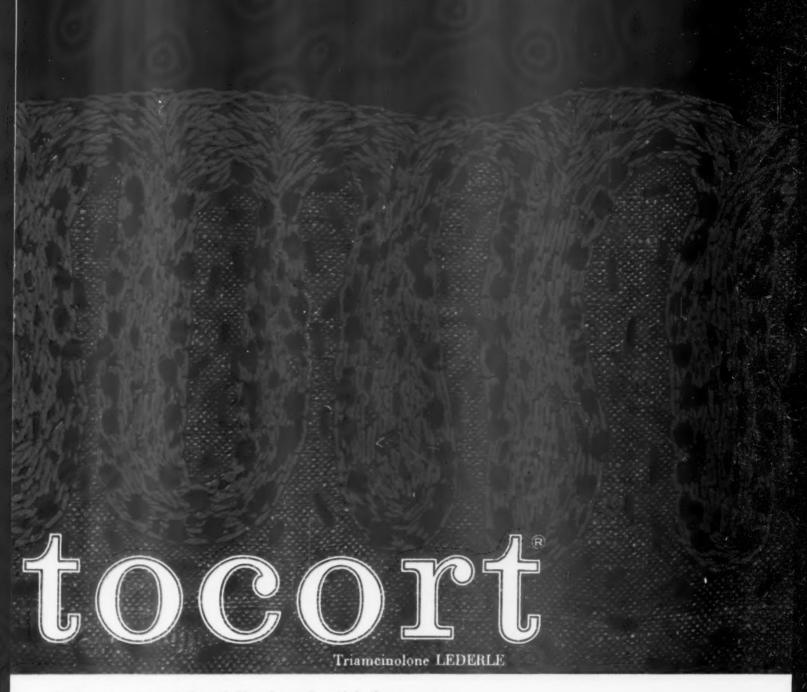
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References: 1. Feinberg, S. M.; Feinberg, A. R., and Fisherman, E. W.: J.A.M.A. 167:58 (May 3) 1958. 2. Epstein, J. I., and Sherwood, H.: Conn. Med. 22:822 (Dec.) 1958. 3. Friedlaender, S., and Friedlaender, A. S.: Antibiotic Med. & Clin. Ther., 5:315 (May) 1958. 4. Segal, M. S., and Duvenci, J.: Bull. Tufts N.E. Medical Center 4:71 (April-June) 1958. 5. Segal, M. S.: Report to the A.M.A. Council on Drugs, J.A.M.A. 169:1063 (March 7) 1958. 6. Hartung, E. F.: J. Florida Acad. Gen. Practice 8:18, 1957. 7. Rein, C. R.; Fleischwager, R., and Rosenthal, A. L.: J.A.M.A. 165:1821 (Dec. 7) 1957. 8. McGavack, T. H.: Clin. Med. (June) 1959. 9. Freyberg, R. H.; Berntsen, C. A., and Hellman, L.: Arthritis & Rheumatism 1:215 (June) 1958. 10. Hartung, E. F.: J.A.M.A. 167:973 (June 21) 1958. 11. Zuckner, J.; Ramsey, R. H.; Caciolo, C., and Gantner, G. E.: Ann. Rheumat. Dis. 17:398 (Dec.) 1958. 12. Appel. B.; Tye, M. J., and Leibsohn, E.: Antibiotic Med. & Clin. Ther. 5:716 (Dec.) 1958. 13. Kalz, F.: Canad. M.A.J. 79:400 (Sept.) 1958. 14. Mullins, J. F., and Wilson, C. J.: Texas J. Med. 54:648 (Sept.) 1958. 15. Shelley, W. B.; Harun, J. S., and Pillsbury, D. M.: J.A.M.A. 167:1590 (July 26) 1958. 17. MeGavack, T. H.; Kao, K. T.; Leake, D. A.; Bauer, H. G., and Berger, H. E.: Am. J. M. Sc. 236:720 (Dec.) 1958. 18. Council on Drugs: J.A.M.A. 169:257 (January) 1959.

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- Bellet, S.; Finkelstein, D., and Gilmore H.: A.M.A. Archives Int. Med. 100:750, 1957.
- 2. Bellet, S.: Amer. Heart J. 56:479, 1958.
- 3. Finkelstein, D.: Penn, Med. J. 61:1216, 1958.

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- "3. The usual dosage of deserpidine was 0.1 mg. three times daily after meals sometimes with an additional dose at bedtime. The average duration of treatment was five months.
- "4. All of the 30 hypertensive patients experienced a reduction in blood pressure, the average fall being 33 mm. Hg systolic and 14 mm. Hg diastolic.
- "5. Of the 29 patients having symptoms of anxiety neurosis, 11 experienced complete relief and 10 partial relief.
- "6. Ten of the 11 patients who had previously experienced undesirable side-effects while under treatment with reserpine tolerated 0.3 mg. or more daily, but 1 tolerated only 0.2 mg. daily. Two patients on 0.3 mg. daily experienced a mild drowsiness, but this did not require stopping or reducing the dose.
- "7. It is concluded that descrpidine is an effective agent for the management of essential hypertension and anxiety neurosis. Benefit appears comparable to that obtained by equal doses of reserpine, but there is a significant and worth-while reduction in the incidence of side-effects."

 Rawls, W. B., and Evans, W. L., Jr., Clinical Experience with Descriptine in the Management of Hypertension and Anxiety Neurosis, New York J. Med., 59:1774, May 1959.

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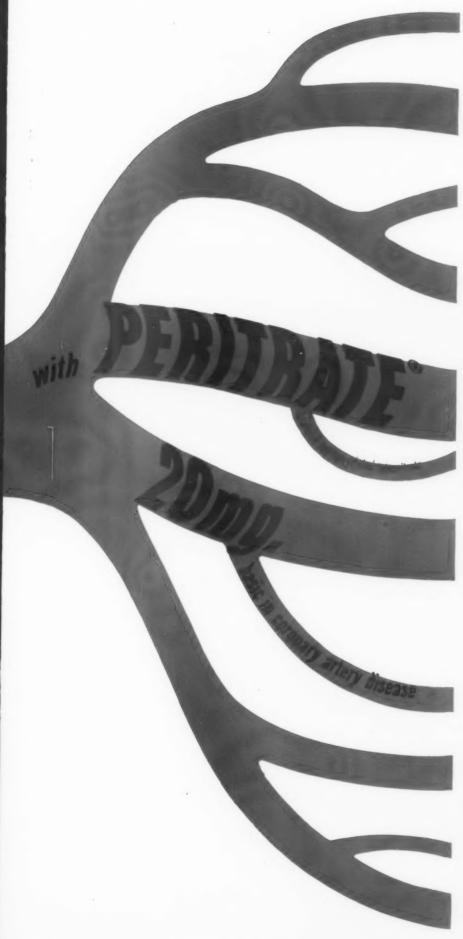
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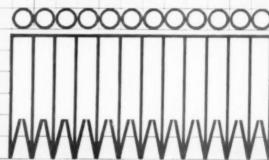
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- Am. Rheum. Assoc., San Francisco, Calif., June 21, 1958.

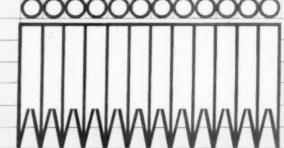
 2. Bunim, J. J., et al.: Paper read before the Am. Rheum. Assoc., San Francisco, Calif., June 21, 1958.

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Armour Pharmaceutical Company Ayerst Laboratories					. ,							,			1	10
Burroughs Wellcome & Co., Inc.	a	a		e						•	٠	٠				90
Ciba Pharmaceutical Products, Inc.	c.			٠												
2	21, 1	Inser	t Be	twee	n Pa	ges 2	24 an	d 29,	84-8	85, !	91, 1.	36-1	137,	For	urth Co	ve
Eaton Laboratories				*							. 1	2-1	3, 1	40-	141, 1 138–1	63
E. Fougera & Co., Inc			,													92
Geigy Company					, ,								11,	33,	103, 1	43
Harvard Medical School Hyland Laboratories, Inc																66
Irwin, Neisler & Co																
Ives-Cameron Company													. 4	9-5	0-51-	52
Lakeside Laboratories, Inc															62-	
Lederle Laboratories, A Division o															154-1	
Thos. Leeming & Company, Inc. Eli Lilly and Company																70
The S. E. Massengill Company .																30
McNeil Laboratories, Inc.											Deta.		. ag	41,	73, 12	26
McNeil Laboratories, Inc. Merck Sharp & Dohme, Division of	of M	1erc	k &	Co	, In	C	4 5				100			2.4	125 1	
															135, 10	
Nordson Pharmaceutical Laborator Nuclear-Chicago Corporation .	ries,	Inc	C.	. ,												76 11
Organon Inc			*											4,	144-14	15
Parke, Davis & Company											67,	112	-11	3, 1	29, 15	53
Pfizer Laboratories Division, Chas.	Pfiz	zer	& C	0.,	Inc.											
Pitman-Moore Company															09, 13	
														_	rd Cov	
Riker Laboratories, Inc					*		*		95	. In:	sert B	etwe				
Roche Laboratories, Division of Ho	ffm	ann	-La	Roo	che I	nc.										
Roche Laboratories, Division of Ho Roerig & Co., J. B.					4	6-47	, 68	-69, 	99, 1	14,	124-	125	, 13	0-1	31, 14 50–15	2
Sanborn Company														,	9	0
Schering Corporation	•				٠		. 3	5, 44	-45,	66,	117,	122	-12	3, 1	59, 16	2
Schieffelin & Company, Inc G. D. Searle & Co													77	7-78	-79-8	ó
Sherman Laboratories															4	U
Smith-Dorsey, a Division of The Wa E. R. Squibb & Sons, Division of M	and	er (Com	pan	y .	Co				18	104	105	10	7 1	82-8	3
Sunkist Growers	lati	nesc.)II C	ilen	ilcai		p.			40,	104	103	, 10	,, 1	3	2
Γhe Upjohn Company U. S. Vitamin & Pharmaceutical C															28, 15	2
Wallace Laboratories Warner-Chilcott Laboratories Winthrop Laboratories Wyeth Laboratories Wynn Pharmacal Corporation									10,	93,	108,	118-	-119	9, 1	32, 16	6
Warner-Chilcott Laboratories					٠	•			•	٠				1, 1	00-16	2
Wyeth Laboratories												2	23, 5	53, 5	58, 14	7
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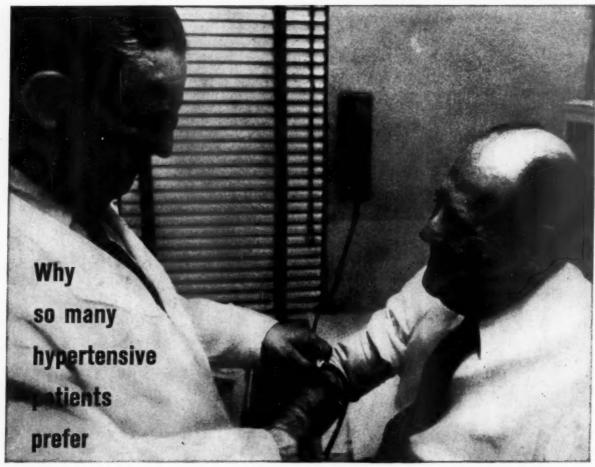
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*Herrmann, G. R., Vogelpohl, E. B., Hejtmancik, M. R., and Wright, J. C.: J.A.M.A. 169:1609 (April 4) 1959.



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